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FATE OF OVA ACCELERATED IN THEIR RATE OF PASSAGE THROUGH THE FALLOPIAN TUBES OF MICE BY MASSIVE INJECTIONS OF PROGYNON-B[1]

H. O. BURDICK AND RAE WHITNEY
From the Department of Biology, Alfred University
ALFRED, NEW YORK

It has been shown (1) that injections of 100 to 500 R.U. of an estrogen, progynon-B in oil, causes acceleration of the rate of passage of ova through the fallopian tubes of mice. This paper is concerned with the fate of such accelerated ova. Experiments here reported show that the uterine environment in these experimental animals produces disintegration of the eggs so that pregnancy is prevented.

METHODS

Each half of the reproductive tract was removed and washed to remove excess blood, then placed in a 0.5 per cent saline solution and the ovary checked for corpora lutea. The uterus was cut immediately below the tubo-uterine junction, then flushed, and the fluid examined for ova. In some cases the uterus still contained seminal fluid with dead spermatozoa and leucocytes 48 to 50 hours after finding the vaginal plug (a.v.p.). The presence of this debris made it almost impossible to find the ova if they had descended well into the uterus. Under such conditions the uterus was hypoemic, elongated, flabby and somewhat distended. As noted in an earlier paper (1) the ova were more often found in the ovarian end of the uterus into which the tip of the tube extends.

The tubes also were checked for ova. If corpora lutea were present in the ovary, but no ova found in either tubes or uterus it was concluded that the ova had disintegrated or were lost in the uterine debris when this was present.

[1] These experiments were made possible by grants from the Penrose Fund of the American Philosophical Society and from the Division of Biology and Agriculture of the National Research Council. The funds were administered by Mr. Curtis F. Randolph, Treasurer of Alfred University.

RESULTS

Table 1 shows typical examples selected from our experiments, some of which were recorded in a previous report. Some photomicrographs were taken to show stages in development and general condition of accelerated ova. The stages in development of the ova and time a.v.p. have been carefully compared with the information on the mouse by Lewis and Wright (2), and found to be in close agreement where the ova had apparently been in the uterus but a short time. It is interesting to note how long the eggs had probably been in

TABLE 1. EXAMPLES OF ACCELERATION[1]

Animal	Time injected a.v.p.	Autopsy hours a.v.p.	Time from injection to autopsy hr.	Tube		Uterus	
				Left	Right	Left	Right
				One injection—100 R.U.			
116	0	49	49	4,3	1	2,2,2	—
130	0	42	42	4	—	2,2,1,1,D	2,2,2,D (Fig. 6)
85	22	51	29	—	4	4,4,4,4,6	4,4,D
129	23	40	17	—	4,4,4,4	—	—
122	31	50	19	1,3	—	—	1,2,2
				One injection—200 R.U.			
111	25	51	26	1,1,1,2,D	—	—	4,4
136	32	56	24	—	—	4,8,8,8,8	8,8,8,8,Z (Fig. 3)
139	32	62	30	—	—	D,D	D,D,D,D,D (Fig 5) (6 to 8-celled)
63	48	59	11	—	—	2,2,2,2	—
67	48	60	12	2,2	—	—	1,2
				One injection—300 R.U.			
57	0	33	33	—	—	2,2,2,2,4 (Fig. 2)	no record
74	3	34	31	2	2,2	2,2,2,2,3	—
75	3	36	33	—	1,1,2,2,2,2	2,2,2	—
60	10	36	26	—	—	2	2,2,2,2 (Fig. 1)
40	11	36	25	—	—	2,2,2,2	2,2
				One injection—500 R.U.			
101	0	37	37	—	—	—	2,2,2
104	0	37	37	—	2	2,2,2,2,2,3,3	—
102	0	38	38	2	—	2,2,4	2,2,3,3

[1] Numbers in columns under tube and uterus refer to stage of each egg. D = pathologic. Z = empty zona.

the tubes, and to determine where they would have been in the tubes under normal conditions.

Keeping in mind that we counted the hours after first finding the vaginal plug, whereas Lewis and Wright count from the time of copulation, we quote from them by way of comparison: ". . . we find that the eggs up to 24 hours are as a rule in the 1-cell stage and in the second loop of the tube. Eggs from 24 to 36 hours after copulation are in the 2-cell stage and in the second, third and fourth loops of the tube. Eggs from 44 to 50 hours after copulation are in the fourth to sixth loops of the tube. Eggs 50 to 70 hours old are in the 8-cell to morula stages and in the sixth loop. Older eggs, late morulae and

blastocysts, are in the sixth loop or uterus." And again, "If we assume that ovulation occurs about the time of copulation" . . . "by 48 hours after copulation almost all are in the sixth or last loops of the tubes. Here they remain about 20 to 24 hours and then pass into the uterus at 68 to 72 hours." Hence the 2-celled ova, collected in the uterus in these experiments, had traveled one to two-thirds the length of the tube 36 to 48 hours ahead of schedule.

It is of further interest to determine the physiological response to

TABLE 2. EFFECT OF MASSIVE DOSES OF PROGYNON-B ON PREGNANCY

Animal	Injection hours a.v.p.	Amount Prog.-B R.U.	Autopsy days a.v.p.	Condition of uterus[1]	Animal	Injection hours a.v.p.	Amount Prog.-B R.U.	Autopsy days a.v.p.	Condition of uterus
154	0	100	7	—	198	7	300	7	—
156	0	100	10	—	194	7	300	8	—
155	0	100	11	—	196	7	300	8	—
157	0	100	11	—	197	7	300	8	—
					64	11	300	8	—
174	0	200	5	+3 blastocysts	65	11	300	8	+. Uterus beaded externally, but no embryos present.
171	0	200	9	—	179	12	300	15	—
172	0	200	9	—					
165	0	200	20	—	180	12	300	15	—
166	0	200	20	—	181	12	300	15	—
167	0	200	20	—					
168	0	200	20	—	175	0	500	7	+?
169	0	200	20	—	178	0	500	7	—
170	0	200	20	—	177	0	500	15	—
					150	16	500	4	—
189	0	300	7	—	151	16	500	11	—
191	0	300	7	—	152	16	500	11	—
193	0	300	7	—	153	16	500	11	—
190	0	300	8	—					
199	3	300	8	—	188	4	1000	8	—
200	3	300	8	—	182	16	1000	13	—
195	7	300	7	—	183	16	1000	13	—
					184	16	1000	13	—

[1] + = pregnant.
— = not pregnant, nor any ova present.

progynon-B, as shown by the time lapse between injections and recovery of ova in the uterus. Table 1 gives some information in the fourth column, but of course the exact time of descent is not known. Either the eggs were or were not present in the uterus at autopsy. In most cases ova were found in the uterus 20 to 30 hours following injections. This would be in line with the uterine response to estrogen as shown by Reynolds and Firor (3). By checking back over our table (1), it appears that the quickest results were obtained when the injections of 100 to 200 R.U. were delayed 24 to 36 hours. In two cases (animals *63* and *67*), where injections were delayed 48 hours, ova were recovered from the uterus 11 and 12 hours later. Animal *129* showed a response within 17 hours, and mouse *122* in 19 hours.

The question arises whether progynon-B directly affects egg development. It has been shown by Burdick and Pincus (4) and Pincus and Kirsch (5)

that small quantities of estrogen do not retard development, but when we look over table 1 we note that, in animal 67, 2-celled ova were found in the left tube. At 60 hours a.v.p. morulae could have been expected. However, this animal was not injected until 48 hours a.v.p., when ova are usually in the 3 to 4-celled stage. Some other factor, such as delayed ovulation, may account for this case. We do not believe now that the estrogen has a direct harmful effect on the early cleavage stages of mouse ova.

At first it was thought possible that these ova reaching the uterus before the morula and early blastocyst stage would, if left undisturbed, continue their development until normal implantation would take place. However, when 5 series of animals were injected once with 100 to 1000 R.U. of progynon-B and autopsied 5 to 20 days later, in only 1 animal were blastocysts found, and that at 5 days a.v.p. In all the others, pregnancy had been pre-

TABLE 3. ANIMALS WITH CORPORA LUTEA BUT WITHOUT OVA—LESS THAN 60 HOURS A.V.P.

Animal	Time injected hours a.v.p.	Amount Prog.-B	Autopsy hours a.v.p.	Corpora lutea	Ova
132	0	100	44	+	−
134	0	100	51	+	−
117	3	100	50	+	−
120	3	100	52	+	−
93	29	100	54	+	−
34	17	200	52	+	−
79	3	300	28	+	−
77	3	300	35	+	−
48	12	300	60	+	−

vented and the ova had disappeared. It is evident, then, even though ova might not have been accelerated, that these large doses of estrogen interfered with the normal course of pregnancy. Table 2 gives the summary of these experiments.

In many cases, ova could not be found in either tubes or uterus, yet corpora lutea of ovulation were present. Table 3 shows some typical cases in which animals were autopsied within 60 hours a.v.p. Occasionally, mated animals were found which had not ovulated. We do not know whether these had mated early in estrus and the large quantities of estrogen present had interrupted ovulation, or whether an anovulatory period would have occurred in spite of injections.

That small injections of estrogen will prevent or terminate pregnancies in some laboratory animals has been well established (6, 7, 8, 9, 10). These early experiments were largely concerned with the effects of estrogen upon the uterine endometrium and the estrous cycle, and not on the fate of the eggs. We are not now prepared to say what effect massive doses of progynon-B have on the uterus, but what our experiments do show is that massive injections of this estrogen cause ova to descend into the uterus before that organ is prepared for them. Even though the uterus should later undergo proper progestational proliferation, pregnancy is nevertheless prevented because of

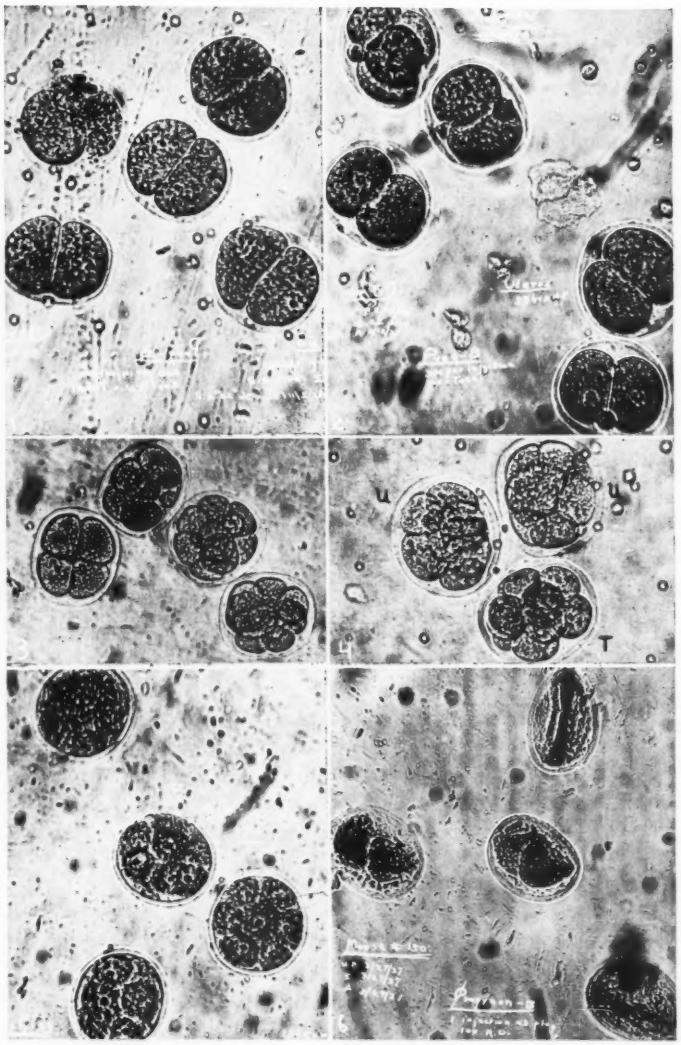

Fig. 1. Mouse *60*. Received 300 R.U. progynon-B at time of vaginal plug. Ova in uterus 36 hours later. ×150.

Fig. 2. Mouse *57*. Received 300 R.U. progynon-B at time of plug. Ova in uterus 33 hours later. Note the prominent nucleoli, polar bodies and the 4-celled stage. Compare the space between blastomeres and zona pellucida with that of ova in figure 1. ×150.

Fig. 3. Mouse *136*. Injection of 200 R.U. progynon-B delayed until 32 hr. a.v.p. Ova just entering uterus 25 hours later. Ova in good condition. ×130.

Fig. 4. Mouse *140*. Injection of 100 R.U. progynon-B at the time of plug and 100 R.U. more 10 hours later. Autopsy 27 hr. a.v.p. Being in the 6 to 8-celled stage the ova are doubtless 50 to 60 hours old. Compare ova found in uterus (*U*) with that found in the tube (*T*). ×150.

Fig. 5. Mouse *139*. Injection of 200 R.U. 32 hr. a.v.p. Ova in uterus in 6 to 8-celled stage at autopsy 62½ hr. a.v.p. Note fused and flattened appearance and loss of contour of blastomeres. Compare with ova in figure 3. ×150.

Fig. 6. Mouse *130*. Injection of 100 R.U. progynon-B at time of plug. Ova in uterus 54 hr. a.v.p. Note disintegration and irregular shapes of ova. ×130.

the previous disintegration of the fertilized ova.

We have been fortunate in getting a series of photomicrographs which show effects of the uterine environment upon ova developing under these experimental conditions. Figures 1 and 2 are of particular interest, because they show ova in the uterus in the 2-celled stage. Both animals had received one injection of 300 R.U. progynon-B. Animal *60* was injected 10 hours a.v.p. and autopsied 36½ hours a.v.p., giving a lapse of 26½ hours after injection. Animal *57* had been injected at the time of the vaginal plug, and autopsied 33 hours later. The presence of a 4-celled ovum indicated that, in relation to ovulation time, the injection was actually later in animal *57* than in *60*. With the exception of one ovum from mouse *60* (fig. 1), all the ova appear normal, but the cytoplasm of the blastomeres is distended against the zona and the polar bodies have disappeared. When the eggs of mouse *60* are compared with those of animal *57* it would seem rather that pathologic changes have actually begun. It has been evident throughout our experiments that massive injections of progynon-B did not appear to affect the eggs while in the tubes.

The eggs from animal *136* (fig. 3) were collected at the extreme tip of the tubal lip which projects into the uterus. These appear perfectly normal, and have apparently just completed the tubal journey. This animal had received 200 R.U. progynon-B 32 hours a.v.p., and was autopsied 57 hours a.v.p., a lapse of only 25 hours after injection.

The eggs from animal *140* (fig. 4) are of interest because two eggs (marked *U*) were collected from the uterus, whereas the third egg (*T*) was found in the lower tube. The differences in the eggs were even more apparent than is shown in the photomicrograph. The tubal egg had clear, sharp, rounded blastomeres whereas those from the uterus began to look fused, flattened, disorganized. This animal had received 100 R.U. of progynon-B at the time of the vaginal plug, and another 100 R.U. 10 hours later. Autopsy was 27 hours a.v.p. The plug, when found, was doubtless older than usual because the eggs were in the 6 to 8-celled stage, indicating that they were 50 to 60 rather than 27 hours old.

The next two figures show more clearly what happens when accelerated ova have apparently been in the uterus for some time. Mouse *139* had received 200 R.U. at the time of the plug, and was autopsied 62½ hours later. By counting the nucleoli these eggs were seen to be in the 6 to 8-celled stage. The pathological condition was evident from the fused appearance of the blastomeres, also the manner in which they flattened out against the zona pellucida and filled the whole cavity. (Compare with the tubal ovum in fig. 4.) These ova look as though they had been kept for a time in a medium having the same density as a 0.1 to 0.2 per cent saline solution. When in approximately the same condition as shown in this figure, the blastomeres will assume a more normal appearance if the eggs are placed for a few minutes in a 0.7 per cent saline or Ringer's solution. This shows that the blastomere walls are still intact.

Figure 6 shows the detrimental effects of uterine fluids in experimental animals. In this animal *(130)*, all the 2-celled ova were collected from the

uterus in a definite pathological condition. Another ovum, in the 4-celled stage and in good condition, was found in the fallopian tube. This should have been included in the photomicrograph for comparison, as it would have indicated that cleavage probably continued in the tubal environment but was inhibited by the uterine fluids. On the other hand, it may be argued that the 4-celled ovum was actually the first to be fertilized but had been reversed in its relative position to the other ova. We have frequently seen ova somewhat scattered in the fluid of the ovarian third of the tube by the muscular contractions in that region. Animal *130* had received 100 R.U. at the time of the plug, and autopsied 54 hours later. If the ova had descended into the uterus within 30 hours after injection, then we can say that destructive processes were well under way within 24 hours after entrance into the uterus.

DISCUSSION

It is evident from these studies that massive injections of 100 to 500 R.U. of progynon-B can cause acceleration of the rate of passage of fertilized ova through the fallopian tubes of mice. That the results are not more consistent has been interpreted before (1) as being due to differences in rate of absorption of the estrogen at the site of injection.

However, it is quite unlikely that estrogen can cause acceleration of ova which were still surrounded by cumulus cells and massed together in the ovarian third of the tube. This would be true, when ovulation occurred late in estrus after coitus. Another factor which might prevent a typical estrogen response would be that the uterus under the influence of old seminal fluid was so elongated, hypoemic and flabby that it could not react to the estrogen. We have frequently seen such uteri after injections, and they differ radically from those of full estrus.

The uterine fluids of these experimental animals are definitely detrimental to the ova, and finally cause their disintegration. These results give us another procedure and explanation of implantation prevention in the early stages of pregnancy. The continued absorption of estrogen from the site of injection probably over-rides the progesterone and keeps the uterus in a state of estrus. We intend running a series of experiments to see if injections of progesterone will enable these accelerated ova to survive. A fuller discussion of some of the physiological factors involved in these experiments will follow this paper in a report on similar experiments with rabbits.

SUMMARY

Acceleration of the rate of passage of ova through the fallopian tubes of mice by massive injections (100 to 500 R.U.) of the estrogen progynon-B results in degeneration of the fertilized ova. This deleterious effect upon the ova appears to be due to a lack of a proper sustaining fluid in the uterus, and not to the direct action of progynon-B.

Acceleration usually occurs within 30 hours after injections. Ova in early cleavage stages show definite pathological changes within 24 hours after entrance into the uterus. Such massive injections of progynon-B will prevent

pregnancy, whether or not acceleration of the rate of passage of fertilized ova has been accomplished.

We are grateful to Dr. Gregory Stragnell of the Schering Corporation for generous supplies of progynon-B.

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ACCELERATION OF THE RATE OF PASSAGE OF FERTILIZED OVA THROUGH THE FALLOPIAN TUBES OF RABBITS BY MASSIVE INJECTIONS OF PROGYNON-B[1]

RAE WHITNEY AND H. O. BURDICK
From the Department of Biology, Alfred University
ALFRED, NEW YORK

Since it had been found possible to accelerate the tubal passage of fertilized mice ova (1), it was decided to try some preliminary experiments on the rabbit. In the mouse, the age of the ova was largely determined by the vaginal plug of mating and by checking against the tables of egg cleavage prepared by Lewis and Wright (2) for that animal. Since the rabbit ovulates 9 to 10½ hours postcoitum, the age of the fertilized ova can be readily determined. Gregory's (3) summary of the cleavage stages of the rabbit are as follows: 2-cell, 22½ hours after coitus; 4-cell, 25½ hours; 8-cell, 32 hours; 16-cell, 40-40½ hours; 32-cell, 47 hours; ovum in uterus about 70 hours after coitus.

METHODS

The rabbits were injected with progynon-B either subcutaneously or intravenously at the hours indicated in table 1. The minimal amount of estrogen, 5000 R.U., was chosen rather empirically, having in mind the mouse-rabbit weight relationship. At autopsy the ovaries were carefully checked for ovulation cones, corpora lutea and hemorrhage areas.

To obtain ova, the technic of Gregory (3) was followed, except that the uterus was severed immediately below the entrance of the tube into the uterus. This made possible the flushing of the uterus from the vaginal end. When flushing the uterus from the tubal end, ova are sometimes lost because the pipette is inserted beyond the region where they lie.

RESULTS

The tubal passage of rabbit eggs was accelerated as it had been in mice. The first animal gave best results photographically because 2 ova were in the right uterus and 1 ovum was in the left uterus 43 hours postcoitum, or 12 hours after injection. In animal *2* the ova were still in the tube. Both animals *3* and *4* were injected intravenously (marginal ear vein), and in neither of these were ova found 50 and 40 hours postcoitum. This has been true for several other rabbits, although definite indications of ovulation have been present.

Figure 1, a photomicrograph of eggs from rabbit *1*, shows 2 ova recovered

[1] These experiments were made possible by grants from the Penrose Fund of the American Philosophical Society and from the Division of Biology and Agriculture of the National Research Council. The funds were administered by Mr. Curtis F. Randolph, Treasurer of Alfred University.

from the uterus (*U*) and one from the tube (*T*) on the same side. The eggs are composed of 12 to 16 cells at 43 hours, which agrees with the findings of Gregory (3). The blastomeres recovered from the uterus begin to show pathologic changes in the cytoplasm, which becomes yellow, whereas the blastomeres themselves appear more irregular and fused. This agrees with our findings on mice ova under similar conditions.[2]

DISCUSSION

In his experiments on the relation of the corpus luteum to implantation in 1928, Corner (4) reported that ova sometimes disappeared 3 to 4 days after

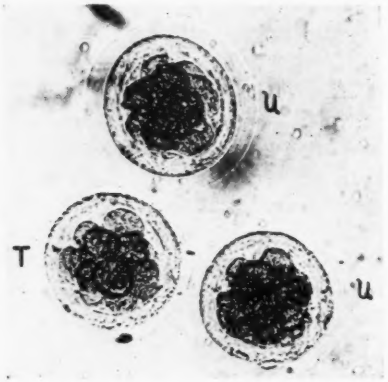

Fig. 1. Rabbit *1*. Received 5000 R.U. progynon-B subcutaneously 31 hr. postcoitum. Two ova found in the uterus at 43 hr. postcoitum. One ovum (*T*) remained in the tube. Compare uterine (*U*) ova with tubal (*T*) ovum. Degeneration of uterine ova has already begun.

the ablation or cauterization of the corpora lutea of rabbits. King, Collins and Peterson (5) attempted to find out why the ova disappeared. These experimenters cauterized the corpora lutea of rabbits and found eggs in the uterus about the usual time, but some showed signs of degeneration. In a second series of rabbits, with cauterized tissue in the body cavity other than corpora lutea, the ova were found to be delayed in development and usually showed signs of disintegration. There is one instance in which degenerate 8-celled ova were recovered from the uterus 48½ hours after coitus, an acceleration which the experimenters suggest might result from an abnormally active tube.

Of course we do not know whether the fertilized ova in our rabbits disintegrated in the tubes or in the uterus, but since the ova in the tubes of animal *2* and the tubal ovum in rabbit *1* all appeared to be normal we do not believe that the ova degenerated in the tubes. Neither does the estrogen delay early cleavage in the tubal ova (6). In view of the evidence of acceleration and degeneration of uterine ova in mice, it is more than likely that a similiar phenomenon takes place in rabbits, but with the difference that rabbit ova in the uterus disintegrate much more rapidly than do mouse ova.

We have tried to correlate the results of acceleration by massive doses of estrogen with tube-locking of ova by injections of 5 to 10 R.U. of the same substance (7, 8, 9), but have not reached a final conclusion. In the tube-locking experiments we assumed that the estrogens simply overrode the activity of progesterone from the corpus luteum, and yet in the presence of much

[2] Compare this figure with those for mice in the preceding paper (1).

more estrogen the ova are not tube-locked but accelerated in passage. Since ova are found in the uterus soon after massive injections (12 to 30 hours in the mouse; 13 to 30 hours in the rabbit) it would appear to be a direct local response of the reproductive tract. We are therefore at present engaged in a series of experiments testing the effects of various hormones on animals castrated after ovulation.

Experiments with mice and rabbits demonstrate to clinicians that there are possibilities of temporary hormonal sterilization (10) through the use of small daily injections of estrogen begun at the time of coitus, and also by single

TABLE 1

Animal	Injection, R.U.	Hours post-coitum for injection	Hours from injection to autopsy	Hours from mating to autopsy	Tube		Uterus		Ovulation
					Left	Right	Left	Right	
1	5000 subcutaneous	31	12	43	2 ova 8-cell	1 ovum 8-cell	1 ovum 8-cell	2 ova 8-cell	+
2	5000 subcutaneous	14	14½	28½	3 ova 4- to 6-cell	9 ova 4- to 6-cell	—	—	+
3	8500 intravenous	36	24	60	—	—	—	—	+
4	5000 intravenous	36	33	69	—	—	—	—	+
5	5000	14½	14	28½	6 ova 6-cell	5 ova 6-cell	—	—	+

massive doses of these substances. To the physiologist is presented additional information on the ovary-tube-uterus relationship. The rather constant 3-day tubal sojourn of the mammalian ovum has been puzzling. It now appears that the life of the early fertilized ovum depends upon such factors as balance of hormones, their time of action, and the physiological conditions of the tube and uterus. Whenever the ovum remains in the tube until the fourth and fifth days, degeneration begins. If the ovum descends into the uterus 24 to 48 hours postcoitum, then the uterus may still contain a mass of dead spermatozoa and leucocytes. Furthermore, the uterus has not yet fully responded to the progestational action of the corpus luteum. The question arises whether the adverse effect upon the ova is due to the quantities of seminal fluid present or to the uterine fluids of estrus. Since, however, we do find degenerate accelerated ova in uteri without seminal fluid, we are inclined to the view that the watery uterine fluid of estrus, or induced prolonged estrus, is responsible for ova destruction. Normally, then, the ova must be held in the tubes until the endometrium changes from an estrus condition to that of proliferation due to progesterone. Nature appears to have hit upon a plan for conserving the life of the fertilized ovum by keeping it in the tube until the uterus is physiologically ready. The tube is the proper embryonic environment until the late morula or early blastocyst (approximately 72 hours postcoitum), but after this time the preservation of the embryo and its subsequent development depend upon the chemicals of the uterus.

Although it may well be argued that the normal animal never would be

subjected to such large amounts of estrogen as used in these experiments, yet the fact that the regular sequence of events in egg transport can be changed is an important fact in itself. Furthermore, some basic physiological factors governing the reproductive tract have been uncovered.

SUMMARY

Single injections of 5000 R.U. of the estrogen, progynon-B, given after ovulation results in the acceleration of the rate of tubal passage of the fertilized ova of rabbits. These accelerated ova in early cleavage stages disintegrate within a few hours after exposure to the uterine fluids, and pregnancy is therefore prevented. These results coincide with those for similar experiments in mice. Some phases of hormonal control of egg transport are discussed.

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CLINICAL INDICATIONS FOR ANTERIOR PITUITARY-LIKE SEX HORMONE

ROBERT L. SCHAEFER, E. A. SHARP AND JAMES V. LAMMY
DETROIT, MICHIGAN[1]

A consideration of the end-results of endocrine therapy does not necessarily involve a technical discussion of the biochemistry of the preparations employed. It is believed, however, that there would be much less confusion in attempts to interpret current endocrine literature if more attention were given to this detail in clinical reports. A brief description of the hormone preparations used in this study will be offered, therefore, and supplemented by a discussion of the clinical indications for their use.

The extract[2] used in the treatment of the cases reported in this paper was obtained from human urine of pregnancy. Its potency is expressed in rat units determined by the induction of corpora lutea within 96 to 100 hours when the extract is injected in 6 doses (twice daily for 3 days) into female white rats 26 days of age. One R.U. is the minimum quantity of urine extract which will cause the formation of one or more corpora lutea under the above conditions. Since the age of the rats, food and other factors modify bioassays of a quantitative nature, rats in this test are selected from a colony the members of which are known to become sexually mature in 50 to 60 days. Furthermore, the accuracy of the assay is enhanced by using a group of 10 or more animals on each dosage and accepting as the minimal effective dose that which induces corpora lutea in 60 per cent of the group.

Clinical Application of Antuitrin-S. The extract from the urine of pregnancy, of the nature described above, is usually regarded as containing follicle-ripening and luteinizing factors. The gonad-maturing action demonstrated in immature female rats offers a presumptive indication for its clinical use. Theoretically, the obvious therapeutic application of this hormone would be in subjects manifesting delayed sexual development. Practical demonstrations of this sex-maturing action of antuitrin-S constitute the basis of this report.

If the action of the anterior pituitary-like sex hormone as outlined in the introduction constitutes a true premise, it is proper to conclude that an immature state of the gonads is a manifest indication for the therapeutic use of this remedial agent.

The 44 cases cited in this report were treated consecutively. All manifested gonadal immaturity. They were private patients, and subjected to a complete diagnostic survey in order to exclude non-endocrine disease.

Genital Hypoplasia and Cryptorchidism. One of the commonest endocrinopathic syndromes is that of adiposogenital pituitarism (Fröhlich's syndrome).

[1] From the Department of Experimental Medicine, Parke Davis & Company, Detroit, Michigan.
[2] Antuitrin-S, Parke, Davis and Company (pregnancy urine extract).

These patients usually exhibit normal growth or statural development exceeding the normal, with girdle localization of adiposity and genital aplasia. In the male, genital aplasia is easily recognized; but in the female, because of the complexity of the genital tract, recognition of variation from the normal is somewhat more difficult. The pre-adolescent female presenting a typical obesity should be subjected to a competent gynecological examination to determine the size of the uterus and adnexa. At adolescence, function should be judged in terms of the menstrual cycle.

Cryptorchidism may or may not be associated with this syndrome. It is not infrequently seen in the normal endocrine type. In our group there were 5 Fröhlich syndromes, 4 of which manifested cryptorchidism in addition to other characteristic physical findings. Two cryptorchids were normal statural endocrine types. One was a case of infantilism. Treatment with anterior pituitary-like sex hormone was indicated in all except possibly the case of infantilism. It is believed that the primary defect in infantilism is in the gonads, which are probably incapable of responding to adequate normal pituitary stimulation. This explanation would account for the negligible therapeutic result in this case. The proper therapeutic approach would be the use of male gonadal hormone rather than a gonad-maturing preparation.

The results in the remaining cases were uniformly good except in *case 1*, which showed normal development of the undescended right testicle at least in so far as size was concerned. The testis was freely movable but could not be expressed beyond the external ring. Surgery should be offered in this instance. The remaining 4 cases all responded with complete testicular descent. In addition, the aplastic genitalia of the adiposogenital pituitarisms were definitely converted into organs of normal size.

Previous to the introduction of the anterior pituitary-like factor, the only corrective for cryptorchidism was that of surgery. At the present time, it might be said that surgery is indicated only after failure of descent following adequate treatment with this hormone, or in the presence of a demonstrable anatomical condition, such as underdevelopment of the scrotum, adhesions, et cetera, which prevent descent.

There is a theoretical objection to the administration of any biological substance capable of producing sex precocity. Induction of premature sex development may produce early epiphyseal closure. Despite this objection, however, it is not contra-indicated at any age level, if employed judiciously for 3- to 6-week periods in the dosage indicated. The patient's progress should be checked from time to time with roentgenographic studies for osseous development. Certainly, there can be no objection to its administration as the age of normal adolescence is approached. No deleterious effect on ectopic testes from the administration of this substance has been reported. On the contrary, current observations have demonstrated not only that descent is induced but that tissue growth is accomplished as well. Opinion as to the ultimate effect on gonadal function of corrected cases of cryptorchidism must be reserved for the time being. In any event, attempt to correct the deformity by endocrinotherapy is desirable, since it is known that cryptorchids usually tend to become atrophic and sterile.

In addition to the anterior pituitary-like factor, other therapeutic measures were indicated in this group. Cases showing obesity and a decreased B.M.R. were given a low caloric diet and thyroid extract to tolerance. These measures consistently induced uniform loss of abnormal localization of adiposity, and brought about a return to a normal body configuration and symmetry. Optimal

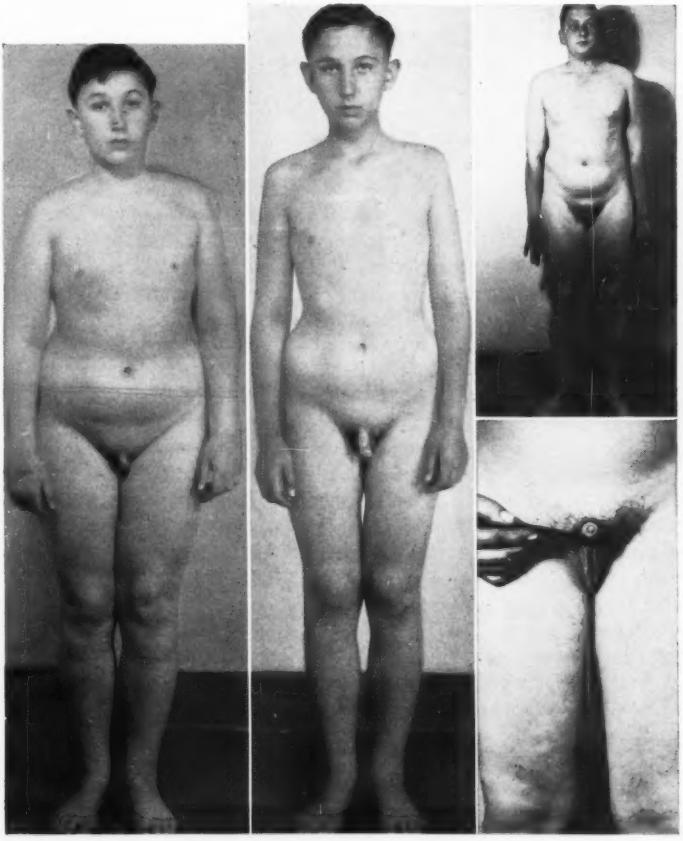

Fig. 1. *Left,* Patient *W.F.,* Fröhlich's syndrome, before treatment; age 11 yr. 7 mo., height 61.6 inches, weight 147 lb. *Center,* After 11 weeks treatment with thyroid extract, Antuitrin-S and low caloric diet; height 62 inches, weight 114 lb.
Upper right, Case 2. *Lower right,* Castration resulting from delayed treatment.

weight loss in the child can be readily secured by diet because of the fact that, unlike the adult, the child has not established fixed bad habits of eating.

Untreated Cryptorchids and Genital Hypoplastics. In the light of present knowledge, it is not only fallacious but may prove vicious for physicians to advise parents of their patients showing cryptorchidism or genital hypoplasia in the pre-adolescent phase of life to follow a course of nonintervention, in the hope that nature will strike a balance, and that all augurs well for the normal sexual future of these children. To show the results of such medical advice, the

following short, abstracted case summaries of 3 young males are cited. Although it may be coincidental, they all were seen within the short period of one month; on the other hand, it also can indicate their possible, not uncommon, occurrence.

CASE REPORTS

Case 1, aged 19 years. Bilateral cryptorchidism was noted by the parents 6 years before. He was examined numerous times by physicians, but no relative advice was given. At the time of examination no signs of normal adolescence were noted, such as change in voice, beard, axillary or pubic hair. Neither testicle was palpable. The scrotum was poorly developed, the penis infantile. His height was 5 feet 7 inches, his weight 150 lb. The patient displayed a beginning type of castrate obesity. There were no suggestive signs of sex function, such as history of erection or nocturnal emissions, and no attraction to the opposite sex. Roentgenographic study for osseous development revealed a delay in epiphyseal closure of 4 years. He was treated for a period of 6 weeks with relatively large doses of antuitrin-S, 5 cc. twice weekly, without any result. Exploratory operation revealed no macroscopic trace of testicular tissue on the right side. Exploration of the left side was advised and will be done.

Case 2, aged 22 years. Complaints and findings were much similar to *case 1,* but, in addition, during the past 2 years there has been a marked development of the castrate type of obesity. A gain of 40 lb. within the past 2 years has occurred. Bilateral cryptorchidism was noted at the age of 11 years. Parents were advised by physicians then and several times since that nature would undoubtedly correct this. Three months previous to our examination he was given competent advice and treatment in the form of 2 cc. of antuitrin-S twice weekly for 7 weeks. He was then referred to our office, and examination revealed both testicles in the scrotum, although each was no larger than a pea and very soft in consistency. His weight was 181 lb., his height 68.2 inches, span 74 inches, upper measurement 32.7 inches, lower measurement 35.5 inches. Roentgenographic study for osseous development revealed a delay of 3 years in epiphyseal closure.

Case 3, aged 25 years. The same signs indicative of sexual immaturity as noted in the above 2 cases were complained of. In addition, there was an exaggeration of the obesity, and gigantism was present. Neglect here can not be placed entirely upon medical advice, as atrophic testicles the size of a small lima bean were palpable in the scrotum. The past history also revealed mumps in early childhood as a possible cause of the production of atrophic testicles. Regardless whether the cryptorchidism was present or not, the genital hypoplasia should have been recognized immediately, as he was repeatedly ill and frequently under a physician's care for many years. The illness consisted of weakness and fainting spells, and was ascribed to his very rapid growth. He has had a few erections but never an emission. Examination revealed a marked eunuchoid giant. His weight was 256 lb., his height 78.5 inches, span 80 inches, upper measurement 36.2 inches, lower 42.3 inches. Roentgenographic study for osseous development revealed epiphyseal closure.

The expectation of being normally sexed as adults is the inherent right of every child. This problem is obviously the duty of the physician, and in no less a degree than the care incident to general health. The ill advice or lack of advice has resulted in tragedy of the 3 above instances. This hormone therapy is apparently an added safeguard in this fundamental function of the physician. At least these conditions should be recognized routinely, and if treatment is of no avail surgery should be resorted to in cryptorchidism.

Amenorrhea. This group consisted of 15 cases, ranging in age from 13 to 28 years. All showed varying types of amenorrhea with a duration from 2 months to 4 years. Four of them also presented a typical adiposogenital pituitarism. Because of the amenorrhea in these cases, it was our opinion that they should be regarded as having gonadal immaturity. Treatment was altered in this series to include theelin in addition to the anterior pituitary-like factor. The extract was given whenever possible for 2 weeks immediately following a period of bleeding, hoping thereby to induce maturation of the follicle with consequent theelin formation. During the 2 weeks preceding the expected menstrual period, theelin was given as a replacement agent. In the event that menstrual bleeding did not occur or, in those cases in which an amenorrhea was present at the completion of our examination, treatment was given in the same manner and then followed by a one-week rest period. The same series of injections were given again and then followed initially by a 2-week and subsequently by a 3-week rest period, in the expectation that the alternation of treatment would eventually coincide with the proper hormonic phase of the menstrual cycle.

Although all patients in this group showed a response to treatment, if we accept establishment of the menstrual cycle as such, it is admitted that the follow-up reports of the cases are not adequate, in so far as time is concerned, to prove maturation of the ovary. Normal ovarian function can naturally be demonstrated only by maintenance of a rhythmic menstrual cycle, conception or fertility over an appreciable period of time.

Menometrorrhagia. It is a common belief that increased menstrual bleeding, whether regular or irregular, cannot be accepted as a sign of increased gonadal function because this type of bleeding is often seen in the younger aged groups. Furthermore, its response in young women is almost specific to adequate therapy with anterior pituitary-like factor.

In the series of bleeding cases included in this report, the age range was from 20 to 47 years. The response to treatment with anterior pituitary-like factor in the first 6 patients cited in table 3 was entirely specific. The abnormally increased bleeding was entirely relieved. From our results we conclude that the beneficient effect of the gonadotropic extract was due to the fact that the bleeding was associated with an immature state of the gonads. The last 4 cases, whose age range is from 40 to 47 years, were treated with larger doses of the anterior pituitary-like factor in order to show by contrast the indifferent or variable effect on bleeding when the gonads are in the menopausal or senescent stage of function.

Menopause. Earlier in our investigations of this hormone, our concept was not so clearly defined as at present. Several cases of menopause which displayed severe menopausal manifestations were treated hopefully. In all instances, treatment resulted in an aggravation of symptomatology. This observation is in agreement with the work of Frank, Kurzrok and others, who showed that in this phase of life there is a proportionately increased amount of this hormone in the blood and urine, with a comparatively decreased theelin content. Therapeutic indications, then, would be an adequate replacement of the follicular ovarian hormone.

TABLE 1. GENITAL HYPOPLASIA AND CRYPTORCHIDISM

No.	Age Adm.	Diagnosis	Size of Genitalia Position of Testicles	Associated Endocrine or Exocrine Entities	BMR %	Therapy		
						Dosage and Type Medicament	Total Dosage	Results
1 *S.D.*	15 Yr. 3 Mo.	Cryptorchidism	Normal size. Left t. normal in size and well-descended. Rt. t. approximately same size and midway in canal.	Roent. study of osseous devel. reveals delay of 2 yr. in epiphyseal closure.	+7	Antuitrin-S 3 cc. 3 times wk. for 4 wk.	36 cc. 3600 R.U.	None. Probably surgical because of disparity in external ring and t.
2 *D.R.*	13 Yr.	Cryptorchidism	Moderate aplasia of penis. Rt. t. fully descended. Left t. just external to the ring.	Normal structural development.		Antuitrin-S 3cc. 3 times wk. for 1½ mo.	54 cc. 5400 R.U.	Left t. fully descended; equal in size to rt. Increase in penile development.
3 *C.R.*	7 Yr. 8 Mo.	AGP[1] plus Cryptorchidism	Size of 3-yr. old. Bilateral crypt. Both t. palpable just above external ring.	Girdle adiposity. Enuresis. Normal osseous development.	−13 −28	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 3 cc. 3 times wk. for 4 wk.	36 cc. 3600 R.U.	Complete descent of both testes. 2-yr. advance in penile growth. Loss of girdle adiposity. Return to normal body configuration and symmetry.
4 *S.J.*	12 Yr. 6 Mo.	AGP plus Cryptorchidism	Size of 7 to 8-yr.-old. T. just outside canal but cannot be brought in to scrotum. Also smaller than normal and soft in consistency.	Girdle adiposity. Normal osseous development.	−29 −35	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 2 cc. 3 times wk. for 6 mo. out of 9 mo.	144 cc. 14,400 R.U.	Pronounced increase in size of testicles. Penis grown, but still some evidence of hypoplasia. Loss of wt. to normal body configuration.
5 *H.L.*	9 Yr. 8 Mo.	AGP plus Cryptorchidism	Slight hypoplasia of penis; size of 6-yr.-old. Left t. descended. Rt. still above external canal; can be palpated above external canal.	Girdle adiposity. Slight delay in osseous development.	−10	Thyroid ext. to tolerance. Ant.-S 3 cc. 3 times wk. for alternate 3 mo. during 1 yr.	216 cc. 21,600 R.U.	After 11 injections testis fully descended. No increase in size of descended testis. At end of yr. penis and testes approximately normal for age. Loss of wt. to normal body configuration.
6 *F.H.*	11 Yr. 8 Mo.	AGP plus Cryptorchidism	Moderate aplasia of both penis and t. T. not descended; just external to ring. Cannot be brought into scrotum.	Moderate girdle adiposity. Thick, dry skin. Pollen allergy. Mental retardation as evidenced by poor school work and physical inactivity. Delay 1 yr. in osseous development.	−18	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 2 cc. 3 times wk. for alternate 3 mo. during 1½ yr.	216 cc. 21,600 R.U.	Full descent of t. occurred after first course of treatment. Continued growth noted; now normal size for age. Normal body configuration and symmetry. Mentally more alert, as evidenced by school work. Physically more active.

[1] AGP = Adiposogenital pituitarism.

TABLE 1. (Continued)

No.	Age Adm.	Diagnosis	Size of Genitalia Position of Testicles	Associated Endocrine or Exocrine Entities	BMR %	Therapy		
						Dosage and Type Medicament	Total Dosage	Results
7 *L.J.*	10 Yr. 4 Mo.	AGP plus Cryptorchidism	Size of 2-yr.-old. Penis lost entirely in mons padding. Scrotum poorly developed. Bilat. crypt.	Obesity. Normal osseous development.	+5	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 5 cc. on alternate days for 3 mo.	225 cc. 22,500 R.U.	Loss of wt. Normal body configuration. Development of scrotum. Penis approximately size of 7-yr.-old. Testicles completely descended after 4 wk. treatment.
8 *W.J.*	12 Yr. 4 Mo.	AGP	Penis size of 4 to 5-yr.-old. T. both descended but proportionately small: extremely soft.	Chronic valvular disease. Girdle adiposity. Normal osseous development.	−10	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 2 cc. 2 times wk. for 5 mo.	80 cc. 8000 R.U.	Increase in size and consistency of testicles. Increase in size of penis. Loss of wt. with normal body configuration and symmetry.
9 *P.G.*	12 Yr. 6 Mo.	AGP	Size of 5-yr.-old. T. comparatively small and soft in consistency.	Girdle adiposity. Normal osseous development.	−11	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 2 cc. 2 times wk. for 6 mo. followed by 4 cc. 3 times wk. for 3 mo.	240cc. 24,000 R.U.	Increase in size of penis, now relatively normal. Definite increase in size and consistency of testicles. Increase noted at end of first 3 months' treatment. Loss of wt. with normal body configuration.
10 *G.B.*	10 Yr. 8 Mo.	AGP	Penis not visible, receding into mons padding. Brought out forcibly and no larger than 1 to 2-yr.-old. T. only slightly better developed.	Girdle adiposity (tremendous). This followed basal skull fracture at age of 5; evidently middle fossa, as there was bleeding from rt. ear. Increased water intake. SDA, .5. Blood cholesterol, 249 mg. Normal ossesous development.	−2	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 4 cc. 3 times wk. for 3 mo.	144 cc. 14,400 R.U.	Very marked increase in genital growth. Penis increased to size of adult thumb. Testicles have increased proportionately and are more firm. Wt. loss of 15 lb.
11 *F.R.*	12 Yr. 7 Mo.	AGP	Size of 3-yr.-old. Both t. descended but proportionately underdeveloped.	Marked girdle adiposity. Normal osseous development.	−7	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 2 cc. 3 times wk. for alternate 3 mo. during 1½ yr.	216 cc. 21,600 R.U.	Approaching signs of adolescence. Definite increase in size of penis and comparable increase in size of testicles. Loss of wt. with normal body configuration.

TABLE 1. (Continued)

No.	Age Adm.	Diagnosis	Size of Genitalia Position of Testicles	Associated Endocrine or Exocrine Entities	BMR %	Therapy		
						Dosage and Type Medicament	Total Dosage	Results
12 *B.R.*	13 Yr. 11 Mo.	AGP	Moderate hypoplasia of penis. T. small and soft.	Adiposity. Mental retardation as evidenced from poor school progress. Blood cholesterol 220 mg. Delay 2 yr. in osseous development.	−6	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 3 cc. 2 times wk. for 3 mo.	72 cc. 7200 R.U.	Increase in size of penis.
13 *S.W.*	12 Yr. 9 Mo.	AGP	Moderate hypoplasia of penis.	Adiposity. Delay 2 yr. in osseous development.	−24 −30	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 4 cc. 2 times wk. for 8 wk.	64 cc. 6400 R.U.	Complete loss of adiposity. Definite penile growth.
14 *R.R.*	10 Yr. 4 Mo.	AGP	Penis size of 2-yr.-old. T. comparable and recede into canal.	Adiposity. Blood cholesterol 222 mg. Normal osseous development.	−31 −16	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 4 cc. 3 times wk. for 6 wk.	72 cc. 7200 R.U.	Testes increased in size; remain in scrotum. Slight increased penile development. Marked wt. loss.
15 *M.W.*	12 Yr. 6 Mo.	AGP	Penis size of 2 or 3-yr.-old. T. size of a bean. Little pubic hair.	Adiposity. Blood cholesterol 190 mg. Delay 1 yr. in epiphyseal closure.	−12 −16	Low caloric diet. Thyroid ext. to tolerance. Ant.-S 4 cc. 2 times wk. for 6 wk.	48 cc. 4800 R.U.	Father, physician, reports increase in size of both testicles and penis.
16 *B.R.*	19 Yr.	Infantilism	Size of approximately 2-yr.-old. Scrotum and t. show only slightly greater growth. Both t. descended.	Eunuchoid type presenting all structural characteristics denoting infantilism.		Ant.-S 2 cc. 3 times wk. for 1 yr.	312 cc. 31,200 R.U.	No change.

TABLE 2. AMENORRHEA

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		Results
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	
1 *W.G.*	13	AGP	11	2 periods in 2 yr.	Marked girdle adiposity and skeletal overgrowth.	−19	Thyroid extract to tolerance. Low caloric diet. Ant.-S 2 cc. 2 times wk. for 3 mo.	48 cc. 4800 R.U.	Followed by 5 normal periods. Loss of weight.
2 *L.J.*	14 1 mo.	−PT	13	Had 8 regular menses. No period since, in 6 mo.	Congenital deformity of hands. Mental retardation. Delay 1 yr. in osseous development.	−16	Thyroid extract to tolerance. Ant.-S 2 cc. daily for 2 wk. after period. Theelin (aqueous) 2 cc. daily for 2 wk. before period. Duration 5 mo.	140 cc. 14,000 R.U. Ant. S 140 cc. 28,000 I.U. The.	After 2 mo. treatment periods were initiated and followed by 5 normal periods.
3 *H.R.*	17 9 mo.	−P	11	28-day interval. 3-day duration. Amenorrhea 1st noted at age of 14. Miss from 2 to 3 mo. Present interval of 7 mo. is longest.	Fainting spells.	−9	Thyroid extract to tolerance. Ant.-S 2 cc. 3 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 3 times wk. for 2 wk. before period. Duration 5 mo.	60 cc. 6000 R.U. Ant. S 60 cc. 12,000 I.U. The.	7 consecutive normal, rhythmic periods. Further check-up reveals there has been a recurrence of amenorrhea.
4 *W.W.*	19	−TP	14	Never regular. From 2 to 9 mo. of amenorrhea. 4 to 7 days in duration, scant.	Marked hypertrichosis of lower extremities; less of upper extremities and face. Normal endocrine type.	−9	Ant.-S 2 cc. 3 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 3 times wk. for 2 wk. before period. Duration 1 mo.	12 cc. 1200 R.U. Ant. S 12 cc. 2400 I.U. The.	Followed with normal period. For 1 yr. treatment was sporadic. Ant.-S or Theelin given as indicated by observer. Had 5 or 6 periods varying from 4 to 10 wk. intervals. Then became pregnant and died, evidently of anemia pregnancy. Full-term delivery. Normal child.

TABLE 2. (Continued)

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
5 *S.H.*	19	—TP	14	1st period consisted of slight stain and persisted for 2 wk. Intervals of 2 to 4 mo. 1st yr. Every 4 mo. had normal flow. In past 2 yr. has had only 1 or 2 periods a yr. Duration of 4 days; normal in amt. Slight dysmenorrhea.	Tall, normal endocrine type. Slight symmetrical enlargement of sella turcica. Normal osseous development.	—6	Ant.-S 2 cc. 2 times wk. for 2 wk. after period. Theelin in Oil 1 cc. 2 times wk. for 2 wk. before period. Duration 6 mo.	48 cc. 4800 R.U. Ant. S 24 cc. 24,000 I.U. The. Oil	3 periods first 6 mo. during treatment. Period every 6 wk. since treatment for 8 mo.
6	19	AGP	13½	Normal 4-day periods for 4 yr. Then beginning of amenorrhea from 2 to 6 mo. Averaged 3 periods a yr. Duration 1½ days.	Girdle adiposity.	—30	Thyroid extract to tolerance. Ant.-S 2 cc. 3 times wk. for 2 wk. after period. Theelin in Oil 1 cc. 2 times wk. for 2 wk. before period. Duration 7 mo.	84 cc. 8400 R.U. Ant. S 28 cc. 28,000 I.U. The. Oil	During treatment had 5 periods, the last 3 in normal sequence. Without medication normal rhythmicity has been established for 1 yr. Loss of weight.
7 *H.P.*	20		18	2 to 3 periods in 1st Year. None in 12 mo.			Ant.-S 2 cc. alternate days for 2 wk. after period. Theelin in Oil 1 cc. alternate days for 2 wk. before period. Duration 2 mo.	28 cc. 2800 R.U. Ant. S 14 cc. 14,000 I.U. The. Oil.	2 normal periods, 1½ days in duration.

TABLE 2. (Continued)

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
8 *S.L.*	22	−TP	13	28-day interval. Duration of 3 days. Decrease in amt. past yr. No menses for 2 mo. preceding exmination.	Anxiety neurosis with depressed state.	−7	Ant.-S 2 cc. 3 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 3 times wk. for 2 wk. before period. Duration 3 mo.	36 cc. 3600 R.U. Ant. S 36 cc. 7200 I.U. The.	Periods normal in amount and rhythmicity for 2 yr.
9 *S.K.*	22	AGP	13	Never regular. Amenorrhea from 2 to 14 mo. Usually 4 days in duration. No period in 3 mo. previous to examination.	Obesity. Hypertrichosis of face.	−9	Thyroid extract to tolerance. Ant.-S 2 cc. 3 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 3 times wk. for 2 wk. before period. Duration 5 mo.	60 cc. 6000 R.U. Ant.-S 60 cc. 12,000 I.U. The.	11 periods in 12 mo. 35 day interval. Increased in amt. Loss of weight.
10 *A.L.*	24	−P	11	Never regular. Intervals from 6 wk. to 3 mo. Duration of 5 days.	Dry skin treated by dermatologist.	+10	Ant.-S 2 cc. 2 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 2 times wk. for 2 wk. before period. Duration 4 mo.	32 cc. 3200 R.U. Ant. S 32 cc. 6400 I.U. The.	4 normal periods all 4 days late.

TABLE 2. (Continued)

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
11 *F.E.*	24	AGP	15	Always irregular except during the 23rd yr. Averages about 4 periods a yr. Duration of 5 days.	Moderate girdle adiposity. Sinus arrhythmia.	−11 −10	Thyroid extract to tolerance. Ant.-S 1 to 2 cc. averaging 3 times wk. for 4 mo.	72 cc. 7200 R.U.	3 normal consecutive periods.
12 *R.G.*	26	−TP	13	1st yr. menstruated only twice. Interval of 4 to 8 wk. 5 to 6-day duration. Scant.	Loss of scalp hair, eyelashes, eyebrows.	−8	Ant.-S 2 cc. 2 times wk. for 5 mo.	80 cc. 8000 R.U.	Followed by 5 normal periods. In 1 yr. 2 mo. menstruated regularly with exception of 1 mo. No effect upon hair-growth.
13 *S.M.*	27	−T	15	Regular up to 23 yr. when appendectomy was done. Amenorrhea total and complete since, for 4 yr.	−G or asthenic type. Skin dry and scaly.	−22	Thyroid extract to tolerance. Ant.-S 2 to 5 cc. 3 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 3 times wk. for 2 wk. before period. After initiation of 1st menses treatment was sporadic and consisted of same dosage of Theelin or Ant.-S as indicated by observer at time. Duration 3 yr.	108 cc. 10,800 R.U. Ant.-S 166 cc. 33,200 I.U. The.	No period until 3rd mo. of treatment. Since then has averaged 10 to 11 periods a yr. for 3 yr.
14 *L.K.*	28	AGP	17	28-day interval. 3 to 5-day duration. At 24 yr. had rapid gain in wt., from 120 to 270 lb. in 6 mo. At that time periods decreased in amt. with occasional amenorrheic periods of 1 mo. No menses in 9 mo. preceding examination.	Girdle adiposity. Chronic cholecystitis.	−3	Low caloric diet. Thyroid extract to tolerance. Ant.-S 3 cc. 3 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 3 times wk. for 2 wk. before period. Duration 7 mo.	126 cc. 12,600 R.U. Ant.-S 84 cc. 16,800 I.U. The.	Loss of wt. In 1½ yr. has missed only 1 period.

TABLE 2. (Continued)

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
15 *H.R.*	33	—TP	14	28-day interval. 4-day duration. Pregnant at 22 yr. Menses irregular since, from 5 days to 2 wk. late. Decidedly less in amt.	Dietetic allergy. Anal pruritis.	—5	Ant.-S 2 cc. 3 times wk. for 2 wk. after period. Theelin (aqueous) 2 cc. 3 times wk. for 2 wk. before period. Duration 4 mo.	48 cc. 4800 R.U. Ant.-S 48 cc. 9600 I.U. The.	5 normal periods. Then 1 period of slight intermenstrual bleeding followed by 2 normal periods.

— P = Hypopituitarism. — T = Hypothyroidism. — G = Hypogonadism. — PT = Hypopituitarothyroidism. — TP = Hypothyropuitarism. AGP = Adiposogenital pituitarism.

TABLE 3. MENO-METRORRHAGIA

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
1 *B.B.*	15	—TP	11	Never rhythmic. Longest interval without bleeding, 3 wk. Frequent periods of profuse bleeding for 5 wk. At examination, bleeding most excessive, necessitating complete bed rest.	Tall, normal endocrine type. Probable juvenile t.b. between 6 and 9 yr.	—20	Treated with iron and thyroid ext. elsewhere for 2 yr. without alteration in bleeding. 4 daily doses of 5 cc. Ant.-S ceased bleeding. Then 4 cc. 3 times wk. for 3 mo.	144 cc. 14,400 R.U.	Cessation of bleeding following 4th dose of Ant.-S. Followed by 2 normally rhythmic but profuse periods. Succeeding 3 periods normal in rhythm and amount.
2 *C.D.*	15	AGP	12	Had 3 normal periods. Amenorrhea for 4 mo. then profuse periods lasting 6 wk. Occur 2 or 3 times a yr. Flowing persistently for 8 wk. when first seen.	Adiposity. Blood cholesterol 185. Advance of 3 yr. in epiphyseal closure. Moderate secondary anemia.	—10 —17	Thyroid ext. to tolerance. Ant.-S 4 cc. 2 times wk. for 3 mo.	96 cc. 9600 R.U.	Immediate cessation of flow followed by 3 normally rhythmic, 5-day periods. Blood picture returned to normal.
3 *P.M.*	20	—TP	13 to 14	28-day interval. 5-day duration. At age of 16, periods came in intervals of 2 wk., persisting to time of examination, but in past mo. has flowed daily.	Moderate girdle adiposity. Gain of 10 lb. in 2 wk. previous to treatment. Acne. BMR requirements not entirely met.	—1	Thyroid ext. to tolerance. Ant.-S 2 cc. alternate days for 1 mo. Then alternate days 2 wk. before each period for 3 mo.	72 cc. 7200 R.U.	Ceased bleeding 1 hr. after 1st injection. 10 normal periods following onset of treatment. Last 7 periods normal without further treatment. Lost 8 lb.
4 *W.M.*	22	—TP	11 to 12	21 to 28-day interval. 5-day duration. Shortly after onset of menses had period of continual bleeding, using 5 to 8 pads daily. 2 wk. before treatment had continual flow with clotting, using 5 to 8 pads daily.	Girdle adiposity.	—27 —26	Thyroid ext. to tolerance. Low caloric diet. Ant.-S 2 cc. 3 times wk. for 2 mo.	48 cc. 4800 R.U.	Loss of weight. Discontinuation of bleeding with 1st injection. Normal, rhythmic periods for 6 mo.

TABLE 3. (Continued)

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
5 *E.M.*	24	—P	17	28-day interval. 5-day duration. Past 3 mo. periods have occurred at intervals of 2 to 3 wk. No increase in amt.	Chronic valvular disease. —G or asthenic type.	+9	Ant.-S 3 cc. on alternate days for 3 mo.	135 cc. 13,500 R.U.	Normal rhythmicity for 10 mo.
6 *G.W.*	27	Subinvolution	13	28-day interval. 5-day duration. Married 3yr. No contraceptives. 2 mo. before treatment gave birth to normal child. Continued uterine bleeding up to time of examination. Retention of secundines ruled out by obstetrician.	Marked anxiety neurosis. Periods of depression.	−3	Ant.-S 3 cc. 3 times wk. for 2½ mo.	90 cc. 9000 R.U.	Gradual discontinuation of flow at end of 2 wk. Since then normal rhythmicity and character of periods for 4 consecutive months.
7 *O.L.*	29	—PT	13	28-day interval. 6-day duration. At marriage, age of 24, missed 2 wk. Then flow continued for 4 mo. steadily. Regular for 1 yr., and same recurred. Past yr. has flowed continuously. Following D and C, bleeding stopped for 1 wk. then continued until time of treatment. No pregnancy. No contraceptives. Tubes patent.	Moderate girdle adiposity.	−13	Thyroid ext. to tolerance. Ant.-S 5 cc. daily for 1 mo. Then 8 cc. daily for 10 days.	230 cc. 23,000 R.U.	Cessation of flow after increased dosage of 8 cc. 2 normal periods followed by pregnancy.

TABLE 3. (Continued)

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
8 *L.M.*	34	—TP	11	24-day interval. 5-day duration. 8 mo. before examination marked increase in amt. with clotting.	Total thyroidectomy 5 yr. preceding. Increase in wt. Chronic colitis.	+9	Ant.-S 2 cc. 3 times wk. for 2 wk. preceding period for 7 mo.	84 cc. 8400 R.U.	6 successive periods normal in amt. No clotting.
9 *W.F.*	40	Probable menopause	13	28-day interval. 4-day duration. Past 2 yr. periods exceedingly profuse. 3 mo. previous to examination flowed continuously for 1 mo. D and C stopped bleeding for 2 wk. then flow continued up to examination time. Pelvic negative.	Tinea cruris. Generalized obesity. Uterine curettings revealed hypertrophic glandular endometritis.	+13 +9	Ant.-S 2 cc. daily for 1 mo.	60 cc. 6000 R.U.	No change in bleeding. Roentgen therapy relieved bleeding.
10 *H.R.*	46	Menopause	13	4-day duration. 4 pregnancies, normal. No change in periods until past 2 yr. Normal rhythm but increase in amt., approaching hemorrhages. Mild menopausal symptoms. Pelvic examination negative.	Blood count within normal limits.	+16	Ant.-S 2 cc. 2 times wk. for 2 mo.	32 cc. 3200 R.U.	No alteration.
11 *R.F.*	47	Menopause	13	28-day interval. 4-day duration. 6 children. No alteration was noted until 2 yr. previous when persistent metrorrhagia began increasing in severity; at time of examination necessitated 3 to 6 pads daily. Pelvic examination negative.	Moderate anemia: RBC 3,500,000 Hemoglobin, 70%.		Ant.-S 2 to 10 cc. daily for 2 wk.	50 cc. 5000 R.U.	No change in bleeding. Patient hospitalized and operated upon. Normal uterus removed. Died 7 days postoperative from embolism.

TABLE 3. (Continued)

No.	Age Adm. Yr.	Diagnosis	Menstrual History		Associated Endocrine or Exocrine Entities	BMR %	Therapy		
			Age at Menarche Yr.	Character and Periodicity			Dosage and Type Medicament	Total Dosage	Results
12 *O.J.*	29	Roentgen Menopause	14	Constant metrorrhagia since onset of menses to time of Roentgen menopause at 23 yr. Resulted in cessation of flow, hot and cold flashes, profuse sweats, fainting spells. 1 x-ray treatment over pituitary.		−2	Ant.-S 1 cc. alternate days for 1 mo. with no relief, but aggravation of symptomatology. 2 cc. Theelin (aqueous) daily for 2 mo. and then as required for 4 mo. Duration 7 mo.	15 cc. 1500 R.U. Ant.-S. 184 cc. 36,800 I.U.	Aggravation of menopausal symptoms with Ant.-S. Relief with Theelin.
13	38	Spontaneous Menopause	13	Essentially negative. Regular to past yr. Irregularity associated with vasomotor instability, mental irritability, gastro-intestinal upsets.	Hypogonad or asthenic type. Tachycardia. Ekg findings within normal. Vague gastro-intestinal symptoms.	+3	Ant.-S 2 cc. 3 times wk. for 2 mo. with aggravation of menopausal-like symptoms. Changed to Theelin in Oil 1 cc. 2 times wk. for 16 mo. Duration 18 mo.	48 cc. 4800 R.U. Ant.-S. 128 cc. 128,000 I.U. The. Oil	Aggravation of menopausal symptoms with Ant.-S. Relief of vasomotor symptoms, mental irritability, tachycardia, and gastro-intestinal symptoms with Theelin in Oil.

— P = Hypopituitarism. — G = Hypogonadism. — TP = Hypothyropituitarism. — PT = Hypopituitarothyroidism.

DISCUSSION

The favorable outcome of cases of Fröhlich's syndrome and cryptorchidism following adequate treatment with antuitrin-S has been previously reported by several observers. Schapiro (1), Sexton (2), Kunstadter and Robins (3), Cohn (4) and others have contributed valuable studies. The convincing observation made by most investigators is the rapidity with which descent of the testes occurs in cryptorchidism after the initiation of treatment. Comparable with this indisputable objective effect in maldescent of the testes is the favorable change in statural configuration observed in Fröhlich's syndrome when adequately treated with the anterior pituitary-like hormone, thyroid extract and diet. Genital growth in the last-mentioned entity may be less dramatic, but in most cases this effect also is quickly induced.

Probably less readily supported is the belief that functional uterine bleeding is the result of gonadal immaturity. That menarche is frequently succeeded by both amenorrhea, hypermenorrhea and polymenorrhea, is generally accepted. A rational conception of the physiogenic cause would appear to be hypopituitarism primarily with consequent gonadal immaturity. Sharp (5) offered this as a working hypothesis for the clinical use of this hormone several years ago. Recently, Fluhmann (6), in discussing the inception of menstruation, pointed out that menarche is neither the beginning nor the end of puberty; rather, that it marks but one event in a period of transition from the years of greatest development to one of full somatic and sexual stature of maturity. He asserted that menorrhagia, metrorrhagia, irregularity, amenorrhea, 'anovulatory cycles' (as described in monkeys) and uterine hemorrhage are all likely to follow menarche. As opposed to radical measures for correcting the menstrual disturbances during adolescence, Fluhmann recommends daily injections of large doses of 'chorionic gonadotropic hormones,' thyroid extract and curettage.

Although it is believed that the major opinion concerning the significance of the puberal period will be in accord with some of the views expressed by Fluhmann, it should be emphasized at the same time that delay in adopting corrective measures for obviously aberrant conditions may defeat their specific purpose at a later period. Lawrence (7) has expressed this thought very well in a recent report "Responsive capacity of the human ovary reaches its maximum during adolescence . . . showing a decided diminution in adult life . . . treatment to be most effective, must be instituted during the prepuberal or adolescent period."

While this precept should govern the attitude of clinicians toward the correction of cryptorchidism alone or associated with Fröhlich's syndrome in the male, Williams (8) has offered statistics recently on the study of undescended testes in a group of institutionalized boys, which showed that spontaneous descent occurred by the 17th year in about 87 per cent of cases. This is an interesting observation, but at the same time the function of the ectopic glands cannot be definitely determined, and even though a greater majority showed spontaneous correction it is, nevertheless, questionable practice to withhold specific hormone therapy with the expectation of favorable changes at puberty.

The assurance of unimpaired gonadal function is greater if descent is induced during either the infantile or juvenile periods of life.

Novak and Hurd (9) reported in 1931 the favorable effect of anterior pituitary-like hormone in controlling functional uterine bleeding. Their initial and subsequent observations, as well as those made by others in the past few years on similar cases, by no means indicate that gonadal immaturity is the sole cause of the bleeding, since antuitrin-S would appear to be effective in menometrorrhagia occurring in later age periods.

Novak favors the association of functional uterine bleeding with hyperplastic endometrium and imperfect luteinization of the follicle due to a deficiency of progesterone. Martzloff (10), on the other hand, points out that endometrial hyperplasia is not the common histologic finding in functional uterine bleeding.

In our experience, as regards the control of menometrorrhagia by antuitrin-S, it is very evident that the hormone is far more effective in the adolescent and young adult than in those of the premenopausal age group. The relationship between gonadal activity, hyperplasia of the endometrium and uterine bleeding constitutes a perplexing problem, but it is our conviction on the basis of clinical experience that the sex-maturing hormone of pregnancy urine is more effective in the younger aged group, for the reason that their menstrual aberrations are more than likely to be the direct result of pituitary-gonad underfunction rather than a sign of gonadal involution.

A word regarding amenorrhea might be offered in this discussion. As asserted above, menarche is usually considered the recognized starting point of reproductive function. Failure of the menstrual cycle early in the postadolescent period is not uncommon, and prior to the development of estrogenic and gonadotropic hormones the methods of treatment were entirely ineffective. According to present endocrine concepts, amenorrhea neither the result of castration nor developmental abnormalities is most frequently due to hormonal imbalance. Although the exact mechanism of the amenorrhoeic phenomenon is not clear, it is generally conceded that amenorrhea of the post-adolescent period is the result of anterior pituitary failure, and in later aged periods is the result of hypogonadism. Underdevelopment of the genital tract may precede or follow amenorrhea; hence, it is desirable to point out that uterine measurements should be made during the diagnostic survey in order to determine whether there is structural deficiency. In the event that uterine hypoplasia co-exists with hormone deficiency, it is believed that the preferable therapeutic procedure is to try and induce uterine growth by large doses of theelin prior to applying gonadotropic hormones.

SUMMARY

Sixteen cases of genital hypoplasia and cryptorchidism, 15 cases of amenorrhea and 13 cases of menometrorrhagia were treated. Results were uniformly good where treatment was indicated, with the exceptions in the text. Competent diagnostic procedures should be instituted to rule out organic disease and also to determine those findings which indicate gonadal immaturity. This will serve the purpose of early recognition, which is of utmost importance in cor-

recting pre-adolescent endocrine imbalances. Pluriglandular treatment is frequently indicated. Secondary thyroid deficiency in this locality can rarely be disregarded. Definite dosage cannot be defined, but must be individualized and thereby adequate to bring about the expected biologic result. Treatment should be prolonged and continuous before concluding that the existing imbalance cannot be corrected. Anterior pituitary-like sex hormone, in our opinion, is the maturing factor of the gonads.

1304 Kales Building, Detroit, Michigan

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OVARIES SECRETE MALE HORMONE. IV. EFFECT OF OVARIAN ANDROGENS ON ACCESSORY SIZE IN THE MOUSE[1]

R. T. HILL AND M. T. STRONG
From the Departments of Anatomy, Yale University School of Medicine
NEW HAVEN, CONNECTICUT
and Indiana University School of Medicine
BLOOMINGTON, INDIANA

It has been well established that in some animals grafted ovaries can furnish sufficient androgens to maintain normal size and function of the sex accessories of castrate males (1, 2, 3, 4)[2] (5, 6). Such results are now produced consistently by Hill (7), and a positive correlation between temperature and androgenic function of ovaries has been proven. Parkes (8) has been successful in obtaining androgenic activity with an extract of pig ovaries.

However, it seems that temperature is probably only a guiding factor in the control of androgenic function of ovaries, a factor which serves to magnify or to bring to the surface a type of physiology potentially incorporated in the constitution of the female gonad. The chemical identity of the reacting androgen from the ovary is still a mystery, but recent evidence leads us to believe that it may be different from that secreted by the testis. Part of that evidence is presented and discussed in this paper, and more will appear soon.

EXPERIMENTAL

Four normal male mice when approximately 40 days of age, received grafts of ovaries in their ears, and were put in a chamber at 20°C. for the next 78 days. This particular thermal environment has been previously shown as being conducive to the androgenic function of ovaries when grafted in the ear. During the first 26 days of this interval they received injections of pregnant mare serum,[3] averaging 12.5 U daily. Three animals (normal males) were treated exactly like the preceding 4, with the exception that no mare serum was injected. These 7 animals were killed at approximately 120 days of age. Their ventral abdominal walls were removed previous to fixation for 24 hours in formalin. The seminal vesicles, with the anterior lobes of prostates attached, were then removed and weighed. The weight of the removed glands averaged 267 mg. It will be noted that the range of weights (205 to 310 mg.) shows no sign of overlapping the range of weights obtained from the control animals.

[1] This work has been supported in part by a grant from the Fluid Research Funds of Yale University School of Medicine to R. T. Hill, and has more recently been granted further support from the Graduate School of Indiana University through Dean F. Payne.

[2] It was unfortunate that in earlier publications Hill and Gardner (6) and Hill (7) did not note these references. These earlier workers had noted the masculinizing effects of ovaries grafted into an occasional castrate male, but did not analyze the problem. Lipschütz (9) has recently referred to his earlier data in a letter to *Nature*.

[3] Gonadin serum was used, and very kindly furnished by the Cutter Laboratories through the courtesy of Dr. D. H. Wonder.

One animal, which carried an ovary grafted into each testis, had accessories weighing 440 mg. at killing. Although somewhat older when killed than the others in the experiment, this animal exhibited an accessory weight much greater than any normal control male, and likewise much greater than any listed by Deanesly and Parkes (8). The weight of the accessories from this animal is not included in the average of table 1. If it be included, then the average is immediately raised from 267 to 288 mg.

The average weight of the accessories from 5 normal control males was 155 mg. (see table 1), with a range from 105 to 172 mg. The controls were of the same age group and of the same inbred strain as the experimental animals.

DISCUSSION

Deanesly and Parkes (10) reported an average seminal vesicle weight of about 245 mg. for normal adult male mice, these weights including that of

TABLE 1. WEIGHTS OF SEMINAL VESICLES AND ANTERIOR PROSTATES

Animal	Treatment, normal males	Mare serum injections	Approx. age at grafting, days	Approx. age at killing, days	Accessory weight, gm.
MSV 55	Ovary in each ear—20° C.	12.5 u daily, 26 days	40	120	280
MSV 56	"	"	40	120	256
MSV 57	"	"	40	120	260
MSV 58	"	"	40	120	310
MSV 60	"	—	40	120	270
MSV 61	"	—	40	120	205
MSV 62	"	—	40	120	286
41 Pg	Ov. in each testis	—	45	265	440[1]
Average: experimentals					267
Controls—room temp. of 24° C.					
S 1				120	172
S 2				120	165
S 3				120	105
S 4				120	165
S 5				120	170
Average: Controls				120	155

[1] Not included in average.

the anterior lobe of the prostate. Weights of the same tissues, taken from the strain of mice used in this experiment, are somewhat less, averaging 155 mg. for 5 animals. The difference in weights of the accessories from individuals was surprisingly small. The fact that in the particular age group used the average for our animals was less than that given by Deanesly and Parkes is not distressing, since our animals are closely inbred,[4] and bear no necessary relationship to the characters existing in the London colony. It is conceivable that sex accessory size may be a character of close inbreeding in a colony of mice.

As previously pointed out by Hill (7), ovaries grafted into the ears of

[4] The very highly inbred mice of Dr. L. C. Strong were used in these experiments (CHI strain).

castrate male mice, when subjected to cool temperatures, will secrete sufficient androgens to cause the development of accessories normal in size and function. The weight given by Hill is approximately 150 mg., and unpublished data further support those findings. The data presented in this paper (table 1) show that normal mouse seminal vesicles and anterior prostates have an average weight of about 155 mg. (for CHI strain only). The reduction of testicular tissue present in a normal male mouse (i.e., unilateral castration) does not affect the gross size of the accessories (11). In view of this we might assume either, *a)*, that the accessories are responsive only to a specific threshold level of testis androgen, or *b)*, that some peculiar body mechanism causes a constant hormone level to be maintained. Hill (6) shows that the presence of a single ovary grafted in the ear seems fully capable of producing sufficient androgens for normal male accessory growth. Much unpublished data in our protocols further support this statement, and lead to the suggestion that the amount of ovarian tissue present is probably not an index of the androgens secreted. At the same time the data presented in table 1 show that, under the conditions of the experiment, the androgenic function of ovarian ear grafts is added to the effect of androgens normally coming from the testis. The weight of the accessories of a castrate male mouse is about 16 mg. (10). The difference between that weight and the average (155 mg.) weight of glands from the normal is 139 mg., a growth response which may rightly be attributed to the male hormone function from the testes. A further step shows that the difference between this weight (139 mg.), produced by testis androgens, and that produced by the male hormone from ovaries plus testes (267 mg.) is 128 mg., and that it must have been produced by the presence of the grafted ovaries. For practical purposes these weights may be considered as equivalent.

We are not inclined to think of any existing synergistic relationship between the ovaries and testes in these experiments, since each gonad can produce a response equivalent to that from the gonad of the opposite sex, and when one organism bears both sets of gonads the effect of one is added to that of the other. Furthermore, since accessory size seems to be unrelated to the amount of gonadal tissue present it is also most interesting and significant to observe double the normal accessory size when testes and androgen-secreting ovaries are present in one individual. These facts lead us to suspect that the male hormone of the testis and the androgens of the ovary are chemically different. If renal elimination or some other body mechanism controls the humoral or body concentration of testis androgens, then that controlling factor must function independently on the androgens from the testis and ovary respectively. If this be the case, then it is further evidence of a chemical difference in these androgens from the male and female gonads. Also, it appears that each substance has a peculiar physiology, in so far as the action of one can be added to the effect of the other; i.e., that they act independently and irrespective of the presence of each other. Further experiments which are in progress relative to thyroid activity lend support to this belief.

The injection of mare serum did not seem to alter in any significant manner the general response of the organism, or the androgenic function of the gonads (ovaries or testes). Further tests in progress, with the use of gonad-

stimulating preparations may possibly lead to knowledge of the part which may be played by various gonad-stimulating agents in the production of androgens by the ovary.

SUMMARY

Experiments have been presented which show that androgens of the ovary act separately and independently from those of the testis. These data lead to the suggestion that the androgens coming from the male and female gonads in the mouse are chemically different substances, but with either closely related or identical physiology.

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EFFECT OF COITUS ON GONADOTROPIC CONTENT OF PITUITARY GLANDS OF PSEUDOPREGNANT RABBITS

A. W. MAKEPEACE, GEORGE LOUIS WEINSTEIN
AND MAURICE H. FRIEDMAN
From the Gynecean Hospital Institute and the Department of Obstetrics and Gynecology and the Department of Physiology, School of Medicine, University of Pennsylvania
PHILADELPHIA, PENNSYLVANIA

Hammond and Marshall (1) demonstrated that rabbits which copulate during pregnancy and pseudopregnancy do not ovulate. Recently in this laboratory, Weinstein and Makepeace (2) showed that the sensitivity of the follicle to gonadotropic material was but little altered during pseudopregnancy. Hill (3) has shown that by the tenth day of pseudopregnancy in rabbits the pituitary contains stores of gonadotropic material much more than sufficient to cause ovulation if discharged. It was with these facts in mind that experiments were planned to test whether the failure of the pseudopregnant rabbit to ovulate after coitus is due to failure of discharge of gonadotropic material from the pituitary.

METHODS AND RESULTS

All animals were kept under the same conditions of food, housing and handling. No animal was used unless its food consumption was constant, both before and during the experimental period. The animals were placed with a vasectomized buck, observed to copulate, and then isolated. On the afternoon of the ninth day, a certain number of these animals, picked at random, were mated with a fertile buck and the occurrence of coitus was verified by the demonstration of sperm in the vaginal smear. Eighteen hours later, the pituitaries were removed both from the females which had copulated and from those which had not been mated. As further controls, pituitaries of 2 types were used, 1 from estrous (postpartum) rabbits and the other from estrous rabbits 24 hours after coitus. The pituitaries of the 4 groups of animals were removed under nembutal anesthesia. The glands were obtained intact, although without the stalks, and stored in acetone at 4°C. until assayed for gonadotropic content.

Before extraction the glands in groups of 3 to 7 were thoroughly dried in a current of air, pulverized, and 8 to 9 cc. of distilled water added per gland. This mixture was held for one hour at approximately pH 8 by the addition of N/20 NaOH, as needed, stirring frequently. The mixture was then centrifuged, the supernatant fluid decanted, brought to pH 7, and stored in a cold place. The residue was re-extracted as above for an additional hour. The two neutralized supernatant fluids were combined, enough NaCl added in order that the final mixture should contain 1 per cent NaCl, and the volume adjusted with distilled

water to equal 20 cc. per gland. Unpublished work by one of the authors (M.H.F.) has indicated that this procedure leaves no detectable gonadotropic activity in the residue. The extract was assayed for gonadotropic content by the method of Friedman (4) and its activity expressed in rabbit units.

TABLE 1. GONADOTROPIC CONTENT OF PITUITARY GLANDS. EXPERIMENTAL AND CONTROL

Type of Donor	Number of Glands	Date of Autopsy	Assay in RB.U.[1] per Gland	
10-day pseudopreg. unmated	3	12/17/36	>30	
	5	10/ 1/37	>20	<30
	19	Scattered over 12 mo. 1935–1936	>25	<30
10-day pseudopreg. Copulation 9th day	4	12/17/36	>20	<30
	5	1/30/37	>15	<20
	7	2/27/37	>35	
Estrous control	3	4/28/37	>20	<30
	4	5/19/37	>20	<30
Estrous animal 24-hr. postcoitum	3	5/ 1/37		< 5
	6	5/31/37	> 2.5	< 5

[1] A rabbit unit equals the amount of gonadotropic substance necessary to ovulate 1 kg. of healthy postpartum rabbit.

Rapid disappearance of gonadotropic substance from the pituitaries of estrous rabbits in the first 24 hours postcoitum, as reported by Hill (3), was confirmed (table 1). This drop in the quantity of gonadotropic material in the pituitary is not found 24 hours after copulation in 9-day pseudopregnant rabbits having functional corpora lutea in their ovaries. The pituitary in this case does not discharge sufficiently (if at all) to be detected under the conditions of the experiment and the method of assay, and certainly not to the extent found after coitus in an estrous animal.

If roughly averaged, the glands of both animals accepting coitus and the unmated controls show a value of 27 RB.U. per gland (i.e., enough to ovulate 9 average-sized rabbits).

SUMMARY

Coitus in the estrous rabbit is followed by a rapid depletion of gonadotropic material in the pituitary gland (confirming Hill). Coitus at the ninth day of pseudopregnancy is not followed by such depletion.

It therefore seems probable that the failure of ovulation in a pseudopregnant rabbit following coitus may fairly be attributed to some failure in the mechanism normally causing discharge of the gonadotropic material from the pituitary.

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ANTIHORMONE STUDIES IN BOYS TREATED WITH ANTERIOR PITUITARY-LIKE HORMONE FOR GENITAL UNDERDEVELOPMENT

GEORGE B. DORFF

From the Endocrine Clinic of the Department of Pediatrics of New York University College of Medicine and the Children's Medical Service of the Third Medical Division, Bellevue Hospital

NEW YORK CITY

The claims of investigators in the field of endocrinology that certain hormones, administered parenterally to experimental animals, will cause a production of antagonistic substances within an animal's blood stream has significance which cannot be overlooked (1). Production of these antagonistic substances or antihormones has been demonstrated in animals for such principles as the maturity, the ketogenic, the thyreotropic and growth factors of the anterior pituitary gland. This demonstration, coupled with the discovery of the APL gonadotropic principle found in the urine of pregnant women, warrants the attention of the laboratorian as well as the clinician (2, 3, 4, 5). Certainly, with the increasing use of endocrine therapy, the clinician must recognize the possibility of the occurrence of such antagonistic bodies in the human (6).

For some time the clinical significance of the likelihood of the existence or production of such antagonistic substances in humans, especially in those receiving chronic endocrine therapy has been considered (7-11). As such, it has led to a study of antihormone response in patients with genital underdevelopment, who were receiving intensive therapy with APL hormone of the urine of pregnant women.

The purpose is not to enter into any detailed discussion on the varied opinions of antihormones, now current on the subject, but to present for consideration the following results from a clinical study.

Nineteen boys, ranging in age from 7 to 13 years, and showing genital underdevelopment varying from the mild form of genital hypoplasia to the severest form of genital underdevelopment, namely intra-abdominal cryptorchidism, were submitted to this study. All of these received hypodermic injections of some commercial brand of APL principle from the urine of pregnant women, either follutein, antuitrin-S, antophysin, or 'A.P.L.'[1] Some received more than one of these brands at different times before tests were made.

The total amount of APL hormone administered to any one patient varied from 11,200 R.U. given over a period of 3 months, to 112,300 R.U., given over a period of 17 months. With the exception of 2 cases, all specimens of sera were taken for examination during the course of treatment with APL hormone,

[1] I wish to express my appreciation to Ayerst, McKenna and Harrison of Montreal, Canada for the supply of 'A.P.L.', to Parke, Davis & Company for the antuitrin-S, to E. R. Squibb & Sons for the follutein, and the Winthrop Chemical Company for the antophysin.

at a time when it was thought that the patient had received sufficient hormone to develop any antagonistic substances. In the other 2 cases, sera were sent for examination, not during, but after treatment with APL hormone had been discontinued for 21 and 24 months respectively. All sera were then tested for antihormone, according to the Collip method by Dr. J. B. Collip, at his laboratory.[2] In all, 20 tests were made on 19 cases, 1 patient undergoing 2 tests at different periods.

Since the patients in this study were receiving or had received hormone apparently sufficient in amount to cause antihormone production, if such were to occur, it was gratifying to find that the sera did not reveal the presence of antihormone. In all 20 specimens, no antihormone could be detected when tested; all sera were negative.

DISCUSSION

It is true that in some of the cases, where marked underdevelopment was present and intensive therapy was administered, there were times when the possible existence of antagonistic bodies was suspected. Occasionally there seemed a relative slowing-up of progress, or even a suggestion of a halt in the development. Dosages were therefore increased, or the product changed, and with these changes the sluggish responses or retardation in progress were overcome, so that progress was resumed, and eventually in most cases the hoped-for results were attained.

It is not certain whether this temporary slowing-up, or halt in progress, which had occurred in some of the cases, was due to a temporary state of antihormone formation, and whether this formation, if existing at all, was then overbalanced by means of increased dosage or by a change to another commercial brand of the same principle. These possibilities are only conjectural. To ascertain whether such antihormone actually forms in humans is more difficult than to speculate on the likelihood that an increase in the dose or a change in the brand of the product might overcome the deleterious effects of these antihormones. If no such effects are to be overcome, and no such antihormone exists, the slowing-up or halt in the progress might be caused by a tolerance in the patient to the particular brand of APL hormone used so intensively. Thus, a change to another brand might have been likely to overcome this tolerance. I believe the latter explanation to be more likely.

There were, however, cases of a severe type, especially those presenting intra-abdominal cryptorchidism and the occasional case of inguinal cryptorchidism, where even increased doses and intensive treatment, or a change of product, failed in any testicular formation or in complete descent of the testes after descent had begun. The possibility of antihormone formation had here also to be considered as a likely cause for the lack of development, were it not for the fact that, although testicular descent could not be accomplished, there was always enlargement and development of the existing hypoplastic gonad, and stimulation and development of the secondary sex characteristics. This was evidenced by marked sexual skin congestion, enlargement and even hypertrophy

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[2] This study was made possible by the kind coöperation of Dr. J. B. Collip, who placed at my disposal the facilities of his laboratory at McGill University.

TABLE 1. ANTIHORMONE STUDIES IN BOYS TREATED WITH APL HORMONE FOR GENITAL UNDERDEVELOPMENT

Patient, Age at outset	Genital Status Prior to Treatment	Preparations used, Total dosage, Period of treatment	Comment
1, *H.L.* 9 yr.	Hypoplastic, migrating testes	Antuitrin-S 19,200 R.U. 5½ mo. (recent tr.)	Also received treatment 2 years ago with 25,250 R.U. follutein over a period of 12 mo., with a fairly good genital response. (7, 8, *Case 12*).
2, *D.B.* 10½	Hypoplastic.	Follutein, antuitrin-S, A.P.L., antophysin. 64,800 R.U. 12 mo.	Complete genital correction.
3, *R.N.* 12	Hypoplastic.	Antuitrin-S 11,200 R.U. 3 mo.	
4, *T.F.* 8	Hypoplastic, unilateral rt. inguinal cryptorchidism.	A.P.L., Maturity factor, follutein 112,300 R.U. 17 mo.	Complete genital correction. (10, *Case 24*).
5, *H.S.* 10½	Hypoplastic, lt. migrating testis.	Follutein, antuitrin-S, antophysin 53,650 R.U. 15 mo.	Complete genital correction.
6, *S.S.* 13⅓	Hypoplastic.	Follutein, A.P.L., Maturity Factor, antophysin 39,800 R.U. 5½ mo.	
7, *J.R.* 10	Hypoplastic, migrating testes.	A.P.L., 30,000 R.U. 3 mo.	
8, *M.B.* 10½	Hypoplastic, lt. intra-abdominal cryptorchidism, rt. testis in scrotum.	A.P.L., follutein 49,100 R.U. 4 mo.	(11, *Case 8*).
9, *P.R.* 11½	Rt. inguinal cryptorchidism, lt. inguinal migrating, ext. genitals fair.	Follutein, antuitrin-S, antophysin, 49,000 R.U. 17 mo.	Testes eventually descended into scrotum.
10, *A.L.* 13½	Hypoplastic, migrating.	Follutein, A.P.L., 21,900 R.U. 4 mo.	
11, *R.S.* 9	Hypoplastic, rt. intra-abdominal cryptorchidism.	Follutein, A.P.L., 42,310 R.U. 4 mo.	Intra-abdominal testis subsequently brought into inguinal canal. (11, *Case 6*).
12, *H.G.* 10	Hypoplastic, rt. inguinal cryptorchidism, lt. migrating, hypospadias.	Follutein, A.P.L., antophysin, 24,550 R.U. 3½ mo.	
13, *H.W.* 13	Hypoplastic, rt. inguinal cryptorchidism, lt. migrating	Follutein, antuitrin-S, A.P.L., 68,050 R.U. 9 mo.	Two antihormone tests done; first after 33,550 R.U. of follutein, and antuitrin-S, 3½ mo. Subsequently complete correction.
14, *G.A.* 11½	Hypoplastic, rt. intra-abdominal cryptorchidism.	A.P.L., follutein, 26,200 R.U. 2½ mo.	Intra-abdominal testis was thought to be felt at internal inguinal ring after 78,500 R.U. in 7 mo. (11, *Case 9*).

TABLE 1. (Continued)

Patient, Age at outset	Genital Status Prior to Treatment	Preparations used, Total dosage, Period of treatment	Comment
15, *H.M.* 11½	Hypoplastic, bilateral inguinal cryptorchidism.	A.P.L., follutein, Maturity factor, 52,600 R.U. 10 mo.	Testes in scrotum. (10, *Case 25*).
16, *J.Ru.* 9½	Hypoplastic, rt. inguinal cryptorchidism, lt., midscrotal.	Follutein, A.P.L., 20,300 R.U. 2 mo.	Subsequently complete correction.
17, *S.G.* 7	Rt. intra-abdominal cryptorchidism, left inguinal cryptorchidism, lt. hydrocele.	Antuitrin-S, 24,900 R.U. 8 mo.	Rt. intra-abdominal testis felt at ring, lt. testis and hydrocele descended into scrotum. (11, *Case 10*).
18, *A.B.* 10	Hypoplastic, lt. intra-abdominal cryptorchidism.	Follutein, 68,000 R.U. 16 mo.	Rt. testis and external genitals developed to normal size, lt. intra-abdominal unsuccessful. (7, 8, *Case 2*, 11, *Case 1*).
19, *M.W.* 10	Hypoplastic.	Follutein, 46,266 R.U. 12 mo.	Complete genital correction. (7, 8, *Case 8*).

'Hypoplastic' refers here to the small external genitals, and testes when present. The 'total dosage' given is that total reached when antihormone tests were made; it is not, in most of the cases, the final total amount of hormone used to correct completely the genital disturbance.

Antihormone tests in *cases 18* and *19* were made 21 and 24 months respectively, after discontinuation of treatment; all other tests were made during treatment.

of the penis, development of the scrotum, and production of suprapubic hair. Such evidences of stimulation and development of the secondary sex characteristics were certainly not indicative of the existence of antihormone even if, in a few of these cases, the cryptorchidism could not be corrected.

Since only 20 tests were made, it would be imprudent to negate the antihormone theory, despite the fact that the blood tests were all negative. But the fact that sufficiently large doses administered over prolonged periods of time could almost always stimulate the external genitalia even though it could not always produce testicular descent, leads one to conclude that this failure does not necessarily indicate the presence of antagonistic substances at work. Even assuming that they might be temporarily preventing progress, the important thing from a clinical standpoint is not so much that they exist but that larger doses of the hormone, or a change to a different commercial brand of the same principle may overcome such a lag.

In all probability, evidences of satisfactory external genital response exclude the likelihood of antihormone in cases where a lag cannot be overcome, or complete testicular descent be accomplished even with intensive therapy. Failure to provoke testicular descent can, most likely, be attributed to true mechanical obstruction rather than to antihormone.

Of the 2 cases out of 19, where sera for antihormone were tested not during but after treatment had already been discontinued for 21 and 24 months, the negative findings lead to the following conclusions. Whereas one might not ordinarily have expected to find traces of antihormone formation resulting from hormonal therapy so many months after this therapy had been discontinued, one might have held the existence of possibly some natural antihormone

responsible for the failure since, in one of these cases, testicular descent could not be accomplished in spite of intensive hormonal therapy. But the sera showed no antihormone, and therefore one is inclined to deduce that, in such cases, even the possibility of natural antihormone, which might upset the natural hormonal balance and prevent normal genital development, is unlikely. A mechanical obstruction is a safer deduction.

SUMMARY

From a group of 19 boys, who had received or who are still receiving hormonal therapy for varying degrees of genital underdevelopment, 20 specimens of sera were taken and studied for the presence of antagonistic substances or antihormone, which might have resulted from chronic treatment with a potent APL hormone derived from the urine of pregnant women. These tests showed that in all cases the sera were free from antihormone.

It is dubious whether the lack of response in some cases was due to the effects of antihormone. The lag or apparent halt in development in some of the cases treated was overcome by increases in dosage, or by a change in the commercial brand of the same principle. In such cases the lag was probably due to a need for greater stimulation from bigger doses, or to a possible tolerance developed to that particular brand of the hormonal product. At least, this was established in most of my cases.

In the few cases of cryptorchidism coming within my experience, where neither an increase nor change could initiate or complete the descent, I believe a true mechanical obstruction existed. I do not believe that this failure was due to the presence of antagonistic substances, since in all these cases satisfactory responses could be provoked in the rest of the genital apparatus.

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CYTOLOGIC EVIDENCE OF THE GONADOTROPIC ACTIVITY OF THE RABBIT'S ANTERIOR HYPOPHYSIS

H. B. FRIEDGOOD[1] AND A. B. DAWSON
From the Department of Physiology in the Harvard Medical School and The Biological Laboratories of Harvard University
BOSTON, MASSACHUSETTS

In 1929, Fee and Parkes reported that removal of the female rabbit's pituitary by decerebration less than 1 hour after mating inhibited the ovulation which would otherwise take place 10 to 12 hours later. If, however, the time between mating and hypophysectomy exceeded 1 hour, ovulation followed within the normal interval. This work has since been confirmed by Smith and White (2). In 1934, Hill (3) demonstrated that the gonadotropic potency of the anterior hypophysis changed abruptly after mating. He found that the anterior pituitary gland of the average normal doe in heat contained 1560 rabbit-ovulating units of gonadotropic substance. One-half hour postcoitum, the gonadotropic potency of the pituitary fell to 1220 U (a 20 per cent decrease); and within 24 hours postcoitum the value had further fallen to 210 U (a decrease in potency of approximately 87 per cent).

One may conclude from these data that rapid functional changes take place in the anterior hypophysis within the first few hours after mating, viz., that within 1 to 2 hours postcoitum the blood stream receives enough gonadotropic hormone from the anterior pituitary to induce ovulation. On the basis of this physiologic evidence, an attempt has been made to determine whether recognizable cytologic changes occur in the gland coincident with the period of its secretory phase. A preliminary report of this work has been published previously (4).

METHODS

Preliminary control cytologic observations were made on the pituitaries from 7 groups of animals, in order to evaluate any changes in the pituitary which might occur subsequent to mating. These groups consisted of *a)*, 5 castrates, *b)*, 5 immature virgins, *c)*, 10 breeding does out of heat, *d)*, 12 isolated estrous does which were not mated, *e)*, 10 estrous does sacrificed immediately after mating, *f)*, 2 does in which follicular growth had been induced with FSH, and *g)*, 17 does in which ovulation had been produced with FSH and LH. Experimental observations were then made on a series of 50 animals at frequent intervals after mating, beginning with 30 minutes postcoitum and extending throughout the period of pregnancy (30 days). The pituitaries of 3 pseudo-pregnant animals were similarly examined. Three male pituitaries were also studied for comparison with those of the females.

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Certain peculiarities in the sex life of the rabbit make it difficult to ascertain the exact reproductive phase of an animal at the time of the experiment. The rabbit has no regular estrous cycle, and mature does are likely to be in estrus if environmental and nutritive conditions are favorable. An anestrous state is usually encountered during the late summer, and similar short periods may occur at irregular intervals during the active breeding season. Young does sometimes allow coitus one or two months before they are able to ovulate. Hammond and Marshall (5) also point out that there is only one certain sign of estrus, viz., characteristic behavior with the buck. The vulvae are usually purple during estrus, but they may be pale. They have been found purple when the doe refused to copulate. Normal coitus, sterile coitus or an orgasm produced by does jumping one another will cause ovulation. In rare instances ovulation has been observed without the introduction of any known stimulus.

Many precautions were taken because of these factors. In particular, all sexually mature animals were isolated for 3 to 4 weeks before being used. When does were not permitted to copulate, their sexual condition was judged by the color of the vulvae and by postmortem inspection of the ovaries and uterus. Complete serial, frontal sections, 4 μ thick, were made of all pituitaries. At first the pituitaries were fixed in Champy's fluid and stained by the method of Severinghaus (6) and by a modified Heidenhain's azan method. This fixative was abandoned in favor of 10 per cent formalin, when it was found that formalin fixation and staining by the azan method made possible the recognition of a third type of granular cell which stained intensively and selectively with azocarmine. Ten per cent formalin, however, did not fix the basophiles and chromophobes adequately. The fixing fluid was then modified to include 90 parts of a saturated solution of corrosive sublimate in physiological salt solution to 10 parts of formalin. This fixing fluid gave excellent and uniform fixation of all the cellular elements and permitted the differentiation of a third type of granular cell, although the contrast was not quite so sharp as after formalin fixation alone (7).

With this fixation and Heidenhain's azan method, the new type of granular cell takes a deep, dark red stain. The ordinary acidophiles are orange, the basophiles deep blue and light blue, and the chromophobes light pink to colorless. The specific cells of the intermedia stain blue, and the chief cells of the pars tuberalis are colorless to light pink. It should be pointed out, moreover, that the pars intermedia may contain both carmine and orange granular cells with a varying number of chromophobes. The intermediate region is not a sharply defined zone, and basophilic cells from this region may be found invading the adjacent tissues of both the anterior and posterior lobes. In addition, the epithelial cells of the irregular cyst-like spaces stain like chromophobes. This epithelium represents the vestiges of the cleft and is sometimes ciliated. The cellular distribution within the pituitary of the rabbit is further complicated by a considerable extension of the tissue of the tuberalis region into the antero-ventral surface of the anterior lobe. This results in a fairly large, irregular zone (zona tuberalis) where acidophiles are relatively sparse and in which either chromophobes or basophiles predominate, depending on the physiological state of the pituitary (8, 9). Occasional acidophiles and numerous basophiles may also be found in the tongue-like projection of the tuberalis as it passes toward the brain in front of the infundibular stalk.

The third type of granular cell, staining selectively with azocarmine, is

a modified acidophile according to the usual classification. Both the carmine cell and the ordinary acidophile cell react with the azocarmine, but the stain is readily extracted from the ordinary acidophile which subsequently takes the orange G. When the staining with azocarmine is omitted both cells stain with orange G. Similarly, when the method of Cleveland and Wolfe (10) is used, the carmine cells also react with orange G. The carmine cells also take the acid fuchsin stain, sometimes more intensely than the ordinary acidophiles (method of Severinghaus, 6). Besides its special tinctorial properties, the so-called carmine cell is further characterized by the relative coarseness and refractivity of its granules. In the other acidophile cells reacting with orange G, the granulation is either very fine, or the cytoplasm may appear almost homogeneous. The macula of the carmine cell (negative image of the Golgi apparatus) is unusually distinct.

Controls

Anterior pituitaries of ovariectomized rabbits. Studies were made of the pituitaries of 5 rabbits, one of which was killed at 2 months, two at 3 months, and two at 4 months after castration. The carmine cells in 4 of these glands were few, small and inconspicuous. In the fifth gland these cells, although still small, were more numerous. At autopsy a small ovarian fragment was found on one side in the animal from which this pituitary was removed. The increased basophilia typical of castration was present in the entire series of glands, but less striking in the doe with the ovarian fragment. The basophiles tended to be concentrated in the medial antero-ventral region or zona tuberalis.

Anterior pituitaries of immature does. The pituitaries of 5 immature does were studied for the occurrence, distribution and condition of the cells reacting specifically with azocarmine. The cells were sparsely distributed in all cases. Usually they occurred as single, isolated cells, although occasionally they were observed in small clusters. The cells were small, not densely granulated, and did not stain intensely. Their distribution was not uniform; they tended to be localized chiefly in the region adjacent to the pars intermedia and to spread laterally and anteriorly along the border of the lobe. They were usually absent in the medial antero-ventral region (zona tuberalis, 11), an area in which acidophiles of either class are rarely found in any considerable number.

Anterior pituitaries from does killed in anestrus. One mature virgin doe and 9 breeding does which refused to mate were included in this group. The pituitary of the mature virgin resembled very closely those of the immature does previously described. There was more variation in the number of carmine cells present in the 9 breeding does, but in 8 the cells were relatively scarce. Usually they occurred singly, but small clusters were also present. The granulation of the ordinary acidophiles and basophiles was markedly reduced. In many respects they resembled the condition obtained after thyroidectomy (12). The pituitary from one doe, killed in June, showed a relatively high number of carmine cells which was about equal to the number of unmodified acidophiles. The carmine cells tend to be aggregated into large groups. The majority of the carmine cells were small, and did not stain intensely; but there was a sprinkling of large, densely stained cells. If the history of this animal

had not been known, it would have been classified, in the light of the cytologic appearance of the pituitary after mating, as one in a state of early stimulation. The ovary showed several normal estrous follicles on histological examination.

Anterior pituitaries of rabbits in which ovarian follicular growth had been induced with FSH. Follicular growth was induced in 2 rabbits by injections of 0.125 cc. of FSH twice daily on 3 consecutive days. The animals were killed 20 hours after the last injection and their pituitaries studied. The carmine cells in both were generally small, scattered and inconspicuous, but occasional large carmine cells were observed.

Anterior pituitaries of rabbits in which ovulation had been induced by injections of FSH and LH. FSH (0.125 cc.) was injected into all 17 animals in this series twice daily for 3 consecutive days, and 0.75 cc. of a mixture of FSH and LH was injected on the fourth day. The animals were killed at intervals varying from 2 to 14 hours after the last injection. Of 11 animals killed between the 10th and 12th hour, only 1 failed to ovulate.

In 4 animals (two killed at 2 hours, and two at 4 hours after the last injection) there appeared to be a mild activation of the carmine cells. They were liberally sprinkled throughout the tissue, and showed a slight tendency to form clusters. However, the typical large, densely-staining cells did not appear. A single conspicuous nodule of these carmine cells was found near the pars intermedia in the pituitary of a fifth rabbit killed at 11 hours. In the other 12 animals the pituitaries appeared entirely quiescent.

Anterior pituitaries of unmated does killed in estrus. Three virgin does in their first period in heat, and 9 breeding does constituted this group. The pituitaries of 3 virgin does showed no significant variation from those in the anestrous state. In the other group, the pituitaries of 4 animals showed minor variations in the number, type and distribution of the carmine cells (fig. 1, 2 and 7). In general, the number of carmine cells was higher than in the preceding groups, but in none was there definite evidence of activation. In 5 others, however, the carmine cells were large, densely stained and massed into rather large, conspicuous areas, giving a picture characteristic of the early period (first hour) after mating (fig. 4). The ovaries of 3 of these animals were examined histologically. One animal had 3 normal estrous follicles, 2 hemorrhagic follicles, and 1 follicle whose ovum revealed maturation changes indicative of stimulation by gonadotropic hormones. The ovaries from the second rabbit contained 9 normal estrous follicles and 1 follicle, probably atretic, which had a first polar body and second polar spindle in its ovum. Three normal estrous follicles and 1 atretic follicle with a first polar spindle in its ovum were found in the third rabbit's ovaries.

Anterior pituitaries of rabbits in estrus, killed within 5 minutes after mating. The 10 rabbits in this group (1 mature virgin and 9 breeding does) were mated before autopsy in order to have positive evidence of their estrous state. The pituitary of the virgin contained only rare carmine cells which were small and lightly stained. In 8 of the 9 breeding animals the carmine cells were more numerous, and in a few instances they were grouped into a sufficient number of small clusters to give a lightly mottled appearance to the anterior lobe. The carmine cells remained relatively small, however, and did not stain

intensely. The ninth doe, a female which had given birth to a litter 12 days previously, was mated and killed 3 minutes later. The carmine cells were found massed peripherally on the dorso-lateral margins of the lobe with scattered clusters in the juxta-intermediate and the central portions. It resembled an activated gland except that the carmine staining lacked intensity.

Experimental animals

Anterior pituitaries of estrous rabbits, killed at intervals varying from 30 minutes to 29 days after mating. Fifty rabbits were included in this series, and for convenience of description they are subdivided into 7 groups, according to the time of autopsy postcoitum. Some does were mated only once, but others had coitus from 2 to 6 times within a period of 5 to 10 minutes. The

TABLE 1. CONTROL GROUP

Experimental condition of rabbits[1]	Number of animals	Extent of carmine cell reaction
Castrated	5	0
Sexually immature	5	0
Breeding does which refused to mate	8	0
	1	±
	1	++
Estrous does isolated for 1 month	7	0
	5	++
Estrous does mated and killed immediately	8	0
	2	+

[1] Refer to text for details regarding animals injected with FSH and LH.

number of matings did not seem to influence the cytological picture of the anterior pituitary so long as ovulation took place. Animals killed less than 10 hours after mating did not ovulate, but in most instances follicular activation could be ascertained by cytological study of the ovaries. Of the 27 rabbits killed 10 hours or more after mating, only 3 failed to ovulate. Two of these were killed at 11 hours, and 1 at 12 hours.

The most conspicuous change in the anterior pituitaries of the mated rabbits is an increase in number, size, coarseness and density of granulation, and intensity of staining of the carmine cells. These cells are not uniformly distributed, but tend to be sharply localized. They may be found in any portion of the anterior lobe except the zona tuberalis. They dominate the cytological picture at the height of the reaction, usually occurring as irregular patches without any definite pattern of distribution. These patches are frequently large, and may even be recognized on the slide with the naked eye. Sometimes only the zone near the pars intermedia is involved. At other times the reaction may be confined to one lateral half, or only a single large nodule of carmine cells may be present. Infrequently, the grouping of cells may be limited and their distribution widespread, thus giving the histological section a reddish mottled appearance. Complete serial sections must always be examined to determine the extent of the reaction.

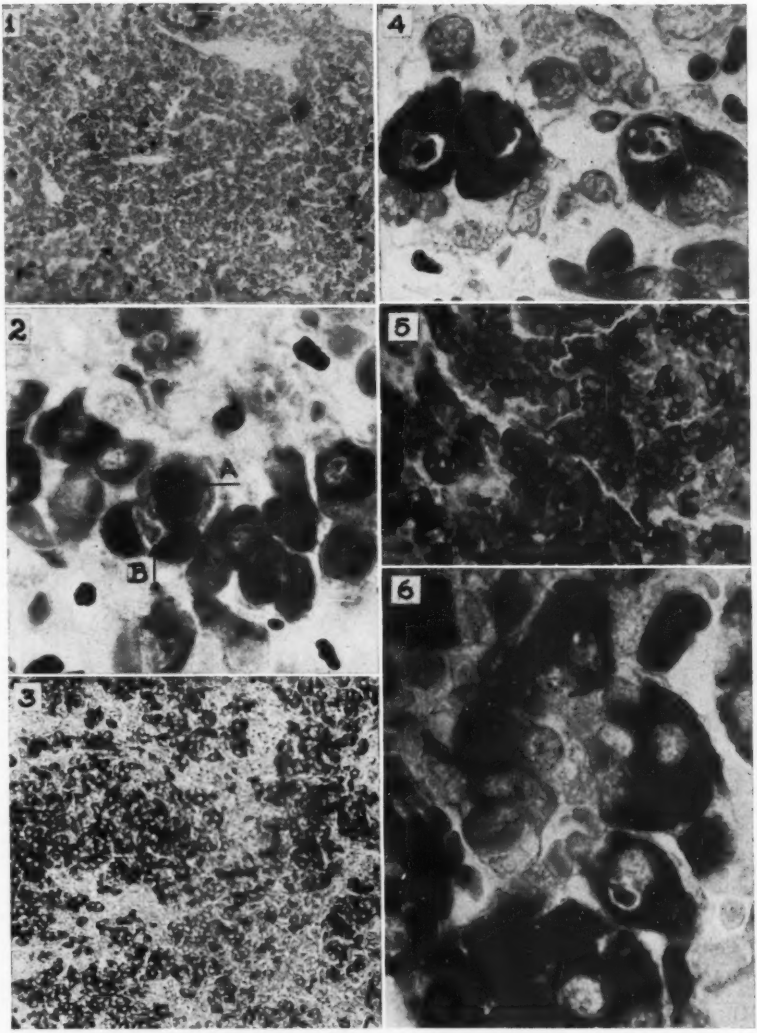

Fig. 1. An area from the anterior pituitary of a rabbit in estrus, showing the characteristic distribution of the carmine cells (black) in an unstimulated gland. ×80. Fig. 2. A small cluster of carmine cells (dark) with a few orange acidophiles (gray) from an unstimulated gland, showing the relative size of the 2 types of cells and the differences in the character of their granulation. A lightly-stained carmine cell is shown in mitosis (A). Note the distinct macula (B) in 3 carmine cells. ×700. Fig. 3. An area from the anterior pituitary of a rabbit 1½ hours after mating, showing the increase in size and number of the carmine cells and the general pattern of their distribution (cf. fig. 1). ×80. Fig. 4. An area from the anterior pituitary of a rabbit in estrus, showing the occasional large, coarsely granulated carmine cells (black) which occur in association with smaller, more finely granulated acidophile cells (gray). ×700. Fig. 5. An area from the same gland as figure 3, showing a dense aggregation of carmine cells with scattered orange acidophiles. ×160. Fig. 6. An area from an activated gland showing densely stained carmine cells (black) and orange acidophiles (gray). ×700.

Tissues in figures 1 and 4 were fixed in formalin. The others were fixed in mercuric bichloride and formalin. All were stained by Heidenhain's azan modification of Mallory's method.

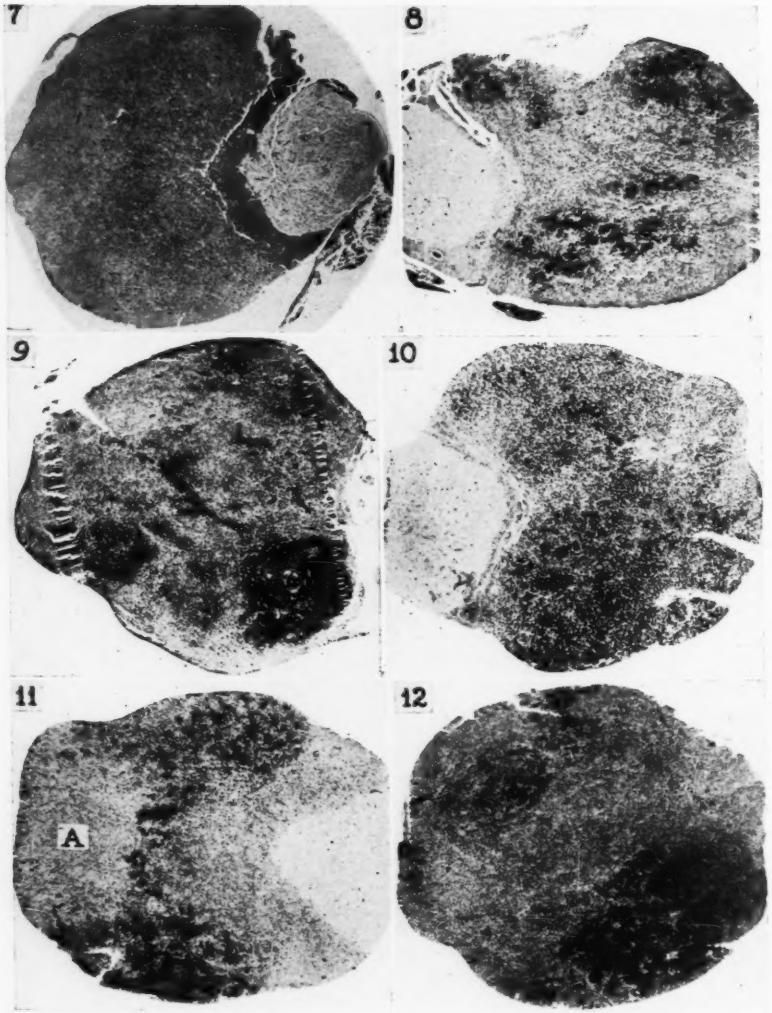

Fig. 7. A representative section of an unstimulated pituitary, showing the uniformity of the cellular distribution in the anterior lobe. ×20. Fig. 8. A section from the pituitary of a rabbit 45 minutes after mating, showing distinct and irregular dense areas of carmine cells. ×20. Fig. 9. A section from the anterior pituitary of a rabbit 3½ hours after mating, showing several dense areas of carmine cells and other regions in which their distribution is more diffuse. ×20. Fig. 10. A section from the pituitary of a rabbit 5½ hours after mating. The cellular aggregations are not so large and distinct. This results in a mottled appearance. ×20. Fig. 11 and 12. Sections of other activated pituitaries, showing variations in the distribution of the carmine cells. In figure 11 the median antero-ventral area, zona tuberalis (A), is distinctly outlined. ×20.

Black areas represent sites occupied by the carmine-staining cells.

Rabbits killed 30 to 45 minutes after mating. There were 6 animals in this series. During this period the appearance of the anterior pituitary is variable, but there is usually definite evidence of stimulation at the end of 45 minutes (fig. 8). The carmine reaction was present in many cells, but they were still small, and accordingly not conspicuous under low magnifications.

Rabbits killed 1 to 1½ hours after mating. There were 7 rabbits in this

TABLE 2. EXPERIMENTAL GROUP.[1] RABBITS MATED AND AUTOPSIED AT VARIOUS INTERVALS THEREAFTER

No. of animals	Time of autopsy hours	Extent of carmine cell reaction	Remarks
4	½	+	
		++	
		+++	
		+++	
2	¾	++	
		+++	
2	1	++	
		+++	
5	1½	++	
		++	
		+++	
		++++	
		++++	
2	2⅙, 2½	+++	
		+++	
2	3, 3½	+++	
		++++	
2	4⅙, 4½	++	
		++	
2	5⅙, 5½	++	R.R.
		+	
2	6½, 8	+	
		+	
2	10, 10½	+	Ov.
		+	R.R.
2	11	+	Ov.
		?	No preovulatory follicles
2	12	0	No ovulation
		+	Ov.-R.R.
2	12½	+	Ov., R.R.
		+	Degr.
2	15	+	Ov., R.R.
		+	Degr.
2	17, 18¼	+	Ov., R.R.
		+	Degr.
2	20, 23½	++	Ov.
		+	Ov.
2	25, 25½	++	Ov.
		++	Ov.
1	47	+	Ov.
1	69	0	Ov.
2	72	+	Ov.
		+	Ov.

[1] Refer to text for details regarding animals autopsied after 72 hours.
Ov. = ovulation; R.R. = reaction receding; Degr. = degranulation.

series. Activation of the gland was consistently evident in all of the animals studied during this interval. In several instances the reaction seemed to be maximal. The carmine cells were large and densely stained and their aggregations were frequently macroscopically visible (fig. 3, 5, 11 and 12).

Rabbits killed 2 to 3½ hours after mating. There were 4 rabbits in this group. The reaction continued to be intense and the areas of carmine cells were sharply outlined in these animals. In general, the maximal reaction occurred in this period (fig. 6 and 9).

Rabbits killed 4 to 8 hours after mating. At this point in the experiment 6 animals were autopsied. The carmine cells remained as large and conspicuous as in the preceding series during the first part of this period. After the fifth hour, however, many of the carmine cells were smaller and showed evidence

of some degranulation. Consequently the pattern of distribution became subdued, and the anterior lobe appeared mottled or diffusely marked (fig. 10).

Rabbits killed 10 to 18¼ hours after mating. Twelve animals made up the material upon which these observations were based. Three animals of this series (2 killed at 11 hours and 1 at 12 hours) did not ovulate. One of the animals killed at 11 hours gave definite evidence of a pituitary reaction; its ovaries contained 8 unactivated normal estrous follicles. The pituitary in the others appeared quiescent. No estrous follicles were found in 1 of these rabbits, and that the animal mated at all is remarkable therefore. In the other animal (killed at 12 hours), the ovaries contained 2 normal estrous follicles and another, possibly atretic, with a first polar spindle in its ovum.

A marked and progressive decrease in the number, size and density of the granulation of the carmine cells was noticeable during this period. The large irregular massing of these cells gradually disappeared; and, in a few pituitaries there was a loss of the staining capacity of the carmine cells with persistence of the chromophilia of the ordinary acidophiles. Differential staining was usually difficult to control in this period, due to degranulation and the loss of the striking color contrast between the two classes of acidophiles.

Rabbits killed 20 to 25 hours after mating. Four rabbits were autopsied during this interval. After the 20th hour postcoitum, the number of large, coarsely granulated carmine cells apparently again increased, but significant aggregations of cells did not occur, so that the sections had a mottled appearance. The cells, moreover, were not as uniformly large and intensely stained as at the height of the reaction, and scattered large cells were frequently associated with numerous smaller and less intensely stained cells in the various cell-groups.

Pregnant rabbits autopsied from 2 to 29 days after mating. There were 11 rabbits in this series. The anterior pituitaries of 5 animals were examined at 2, 2⅞, 7, 15 and 29 days, respectively. Two animals were killed on each of the 3rd, 16th and 21st days, postcoitum, and their pituitaries studied in the usual manner.

Large, conspicuous carmine cells were rarely seen in the pituitaries of animals autopsied between the second and third day, but numerous tiny clusters of small, less intensely stained cells were present. Nevertheless, large carmine cells were present in the animal killed at 7 days postcoitum. They were relatively numerous and occurred in association with the clusters of the smaller type. The carmine cells were rarely found at 15 and 16 days postcoitum, but the pituitaries presented a lightly mottled appearance due to the staining reactions of the clusters of small cells. During the later days of pregnancy, 21 to 29 days, there was little change in the appearance of the carmine cells. They were usually small, but in one animal killed at 21 days tiny groups of typical large carmine cells were found scattered through the clusters of small cells.

Anterior pituitaries of pseudopregnant rabbits. The pituitaries of 3 rabbits in late pseudopregnancy were examined. The carmine cells varied in number, were small and lightly stained. They showed no evidence of the usual postcoital activation.

Anterior pituitaries of male rabbits. The pituitaries of 3 adult male rabbits were also studied. The carmine cell was usually found to be very rare, small and inconspicuous. In one animal, however, a single small cluster of large cells was found. These cells were limited generally to a narrow zone adjacent to the pars intermedia. The basophilia in the males was surprisingly high, equaling, if not exceeding, that of the castrated females. These males had been isolated for at least a week prior to their autopsy.

Occurrence of mitosis in the anterior pituitaries of adult rabbits. During the course of the examination of 135 pituitaries, only 4 cells (3 carmine cells and 1 basophile) were seen in mitosis. The dividing acidophiles were found in the following animals: 2 females in which ovulation had been induced by a mixture of FSH and LH (examined 2 and 14 hours after the last injection); and one animal in the third week of pregnancy. The dividing basophile was found in an animal which was 16 days pregnant.

DISCUSSION

One may conclude from this study of 114 rabbits that the anterior pituitary contains a cell, the contents of which are specifically stained by azocarmine after formalin fixation. A similar, but not morphologically identical, cell has been found in the pituitary of the adult female cat (9). The control group of the present investigation consisted of 61 rabbits in 7 different physiological states, and the experimental series included 53 does, 50 of which were killed at specified intervals after mating, and 3 of which were autopsied late in pseudopregnancy.

There was a clean-cut difference in the results obtained in these 2 groups. Only 6 of the 61 control animals showed well-circumscribed, conspicuous areas of large, densely stained carmine cells. Five of the 6 came from animals evidently in estrus; the other one was removed from a breeding doe which refused to mate. There were no large carmine cells (activated form) among the castrates and immature does. On the other hand, all of the 23 animals autopsied between 45 minutes and 8 hours postcoitum showed evidence of activation. The reaction was strongest from 1 to 3½ hours postcoitum, after which obvious degranulation occurred and the carmine cells were found to be isolated, smaller and much less conspicuous. After the 20th hour postcoitum the number of large, coarsely granulated carmine cells were found to be increased in the four pituitaries examined at this time, but significant aggregations of cells did not occur.

Conclusions have not been drawn with reference to the period which extends from the 2nd to the 29th day of pregnancy. The limited data (11 animals) permit one to infer only that carmine cells are present during pregnancy in varying numbers. They appear to be at a minimum during midpregnancy, and in no instance does the pituitary show anything resembling the immediate postcoital activation.

The varying capacity of the pituitary to induce ovulation has been studied by Hill (3) in relation to the different phases of the reproductive cycle. His data show that the greatest storage of ovulating substance in the pituitary occurs at estrus and in the middle of pregnancy, periods at which the num-

ber of large carmine cells usually approaches a minimum. The maximal carmine reaction, on the other hand, is correlated with the period of rapid release and disappearance of the hormone from the gland. It is of interest that a secondary carmine reaction may be present at a time when it is known that functional corpora lutea are being established.

These data reveal a remarkable parallelism between the gonadotropic activity of the anterior hypophysis and the presence of the activated form of the carmine cell. The possible exceptions to this conclusion may be more apparent than real. The presence of large carmine cells in the pituitaries of unmated estrous rabbits is to be expected. The normal rabbit goes into estrus because the pituitary secretes sufficient gonadotropic substance to maintain adequate follicular development. Presumably, the gonadotropic hormones are elaborated by, or released from, the carmine cells present in the pituitaries of the unmated estrous does. There is considerable variation in the number of such carmine cells present in the pituitary at estrus. Since there is no quantitative method of gauging the intensity of the rabbit's libido (which obviously fluctuates from time to time) we were unable to correlate the extent of the carmine-cell reaction with the intensity of estrus. In this connection it may be significant that the ovaries were exceptionally large and contained unusually conspicuous estrous follicles in 2 of the unmated estrous does whose pituitaries showed an extensive carmine reaction. It seems probable, also, that the previous reproductive history of the animal may be responsible for some of the less striking differences. In many of the glands stimulated by coitus there were significant differences in what we thought to be the maximal reaction. This may have been related to differences in the breeding experience of the does. Accordingly, so far as the ovulatory response is concerned, it may be that the relative increase in the number and size of the carmine cells rather than the absolute number present is the important feature of the activated gland.

In general the preponderance of evidence has indicated that the basophile cells of the anterior pituitary are concerned in the production of the gonadotropic hormones. The present study, however, offers evidence that the acidophile group may also be involved. Cells reacting with azocarmine are found in all the pituitaries of normal mature females, and appear, on the basis of their staining reactions, to be derived from what might be termed the ordinary acidophiles. Their massed arrangement in the activated gland, however, precludes their derivation solely from any one cell type. It is possible that they arise directly from chromophobes as well as by the modification of the common acidophile type. Transitional stages, between cells staining with orange G and those staining with azocarmine, have not been recognized, although the size of granules and intensity of the carmine reaction may vary. When the reaction is receding cytologically, the carmine cells become degranulated and eventually resemble small chromophobes.

Other observations also suggest a participation of acidophiles in the production of the gonadotropic principle. It has been observed repeatedly that after thyroidectomy there is an increase in the size of all the glandular cells of the anterior pituitary in the rabbit, with a decrease of the stainable acidophile

granules which may progress to complete disappearance by the 60th day (12). These changes have been confirmed also by van Dyke and Chen (13), who found in addition that the total content of ovulation-producing hormone of such glands was usually decreased.

Wolfe, Phelps and Cleveland (8) have made a quantitative analysis of the cell numbers of the rabbit pituitary at estrus and during pseudopregnancy following sterile copulation and induced ovulation. Their staining technique did not differentiate the carmine cell from the ordinary acidophile, and the time intervals of 24 hours were too long to permit a close comparison of their observations with ours. Their data, however, suggest that changes in both basophiles and acidophiles may be involved in modifying the capacity of anterior pituitary to produce ovulation.

In a recent review of the cellular changes in the anterior pituitary Severinghaus (14) has marshalled considerable evidence, chiefly from sources other than observations on the rabbit, that the assignment of gonadotropic function to the acidophiles is not without support. He further suggests in this regard that the basophiles produce the follicle-stimulating (FSH), whereas the acidophiles produce the luteinizing hormone (LH).

We are not yet in a position to discuss the precise physiological significance of the carmine cell. Its presence in the anterior pituitary of the rabbit is obviously related to the gonadotropic functions of that gland. There are various possible explanations for its presence and the remarkable changes which take place in its appearance during the active postcoital phase of the gland's gonadotropic activity. The carmine cell may represent physical evidence of secretion alone, or it is possible that both elaboration of hormone and secretion are going on simultaneously. If this is the case, it would appear that the observed localized reactions may represent temporary storage areas, which, as they discharge their secretion, are progressively succeeded by other areas likewise storing and then discharging. Thus successive areas of the gland might eventually be involved in elaboration and elimination. This interpretation is supported by the cytological appearance of the glands at 12 to 18 hours after mating. In these glands the number of ordinary acidophiles is greatly reduced, and small degranulated carmine cells predominate. In other words, the presence of localized areas of reaction may represent merely a cross-section of a continuous process whose loci of activity are continuously shifting until the reaction is terminated.

SUMMARY

Isolated, small carmine-staining cells can be found in the pituitaries of castrate and immature rabbits. They contribute insignificantly to the cytological make-up of the anterior pituitary gland in such animals. Their number appears to be increased in animals approaching sexual maturity, and may occasionally be fairly prominent in the pituitary of the estrous rabbit. These cells really dominate the cytological appearance of the gland only after mating. They become markedly enlarged and increased in number. The size, density and coarseness of granules are markedly increased; and the cells take a deeper, more striking carmine stain. Usually they are not uniformly dis-

tributed throughout the pituitary, but tend to become aggregated into circumscribed areas which are sharply localized.

Rapid functional changes take place in the anterior pituitary within the first few hours after mating. It is known that within 1 to 2 hours postcoitum the blood stream receives enough gonadotropic hormone from the anterior pituitary to produce ovulation. The carmine cell is a prominent feature of the anterior pituitary during this phase of the gland's gonadotropic activity. Its precise relation to the pituitary hormones which are known to be secreted at this time is as yet not clear.

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INSULIN SHOCK IN RELATION TO THE COMPONENTS OF THE ADRENALS AND THE HYPOPHYSIS

H. G. SWANN AND J. W. FITZGERALD
From the Department of Physiology
University of Chicago
CHICAGO, ILLINOIS

Adrenalin, by its hyperglycemic action, is known to antagonize the hypoglycemic effect of insulin and hence to prevent or diminish insulin shock (1, 2). Furthermore, that an increased discharge of adrenalin occurs in insulin hypoglycemia, thus helping to withstand the upset in homeostasis, was shown by Cannon, McIver and Bliss (3); this important observation has been confirmed by Abe (4), Houssay, Lewis and Molinelli (5), and Pijoan (6), but Stewart and Rogoff (7) dissent. Still another method of indication that the adrenal medulla acts antagonistically to insulin is that of inactivation of the gland by denervation, followed by the administration of insulin. Such animals have been found from 4 to 10 times more sensitive to insulin than the normal by Cannon, McIver and Bliss (3), Britton, Geiling and Calvery (8), Sahyun and Blatherwick (9), Dworkin (10), Barnes, Scott, Ferrill and Rogoff (11), and Freeman, Smithwick and White (12).

Since total adrenalectomy causes removal of both medulla and cortex, it might be expected that such animals would be hypersensitive to insulin. This has been found to be true by Sundberg (13), Lewis (14), Lewis and Magenta (15), Hallion and Gayet (16) and Ohmi (17); these workers report in general decreases in resistance to insulin after adrenalectomy, to levels from one-fourth to one-tenth of the normal. Lewis (14) and Artundo (18), employing adrenalectomized rats, indicate that this animal is 10 times more sensitive to insulin than the normal. Artundo's rats (18), if they did not succumb to adrenal insufficiency, gradually became less sensitive to insulin; they never, however, completely regained their pre-operative resistance.

In summary, it appears that any tampering with the adrenals or their innervation leads to an increased sensitivity to insulin. Denervation and demedullation by curretage probably come very close to inactivating the medulla completely; nevertheless, the possibility of all secretion of adrenalin is not excluded by such operations. The technic of adrenal transplantation in the rat offered an opportunity to test animals with no medullary tissue, since it has been found by many (19, 20, 21) that in these transplants only cortical tissue takes.

The discovery of Houssay and Magenta (22) that hypophysectomy leads to increased sensitivity to insulin has been abundantly confirmed (23). But extracts of both the posterior and anterior lobes exert hyperglycemic effects

(24, 25). Both of these hyperglycemic agents have been found to antagonize the hypoglycemic and convulsant effects of insulin.

In order to determine which portion or portions of the hypophysis actually antagonizes the convulsant action of insulin, attempts surgically to remove either the posterior or anterior lobe singly have been made. Geiling, Campbell and Ishikawa (26), reporting such an attempt in the dog, considered the posterior and not the anterior lobe as the important antagonist to insulin in the pituitary complex. No postmortem verification of their operative technic was, however, reported. Houssay and Potik (27), by implantation technics indicated that in the toad only the anterior lobe exerts an insulin-antagonistic action. Pencharz, Cori and Russell (23) showed that in the rat, where complete removal of either anterior or posterior lobe can be readily accomplished, only the anterior lobe antagonizes insulin. Removal of anterior lobe only caused an insulin sensitivity similar to that of total hypophysectomy, whereas removal of the posterior lobe left the rats with a normal resistance to insulin. Our results entirely confirm those of Pencharz, Cori and Russell, but it is thought worth while to present them as confirmation and also as additional quantitative details.

METHODS

Mature rats were used. Adrenals were either totally removed or else removed and then transplanted to the ovaries. After testing, the transplants were removed by an ovariectomy. Histologic examination of the transplants were made in order to ascertain the presence or absence of medullary and cortical tissue.

Removal of the whole hypophysis or the posterior lobe only was done by the method of Pencharz, Cori and Russell (23). Histologic examination of the contents of the sella turcica after autopsy also confirmed the completeness of the operation.

Totally adrenalectomized rats were kept in good health by a diet including bread and milk, with one-half per cent sodium chloride as drinking water (28). The functional proof of the completeness of the removal of the adrenals was furnished by removal of the sustaining diet. If all the rats died after the bread, milk and salt were removed from the diet, then none of the animals had left in them sufficient cortical tissue to maintain life. 'Fox-chow' was used as the replacement diet.

The insulin sensitivity of all rats was measured by determining the minimum dose needed to cause convulsions. The insulin[1] was injected intraperitoneally in a volume of approximately one cc. of water, after the rats had been fasted for 12 to 16 hours. If convulsions ensued, the rats were relieved with concentrated glucose administered by stomach tube under light anesthesia. The rats were considered as being in convulsions when there were observable rapid clonic contractions of the whole body musculature, often with rolling movements.

By trial and error, the per kilogram quantity of insulin was found which would just cause convulsions (here called the 'convulsant dose'). Two doses were ascertained, one of which would just cause convulsions in a given rat,

[1] The insulin used in this study was generously supplied by Dr. Clowes of Eli Lilly and Co.

and a smaller one which would not. Thus, if a rat were thrown into convulsions by 0.8 U but not by 0.6 U, then the convulsant dose was 0.8 U. The difference between these two doses was 0.5 U for insulin, administered in quantities over 1 U per kg. and 0.2 U or less for insulin administered in quantities under 1 U per kg.

RESULTS

In figure 1 is shown the convulsant dose of insulin of all groups of rats. The range, number of animals, and average convulsant dose of the group are indicated.

A). Normal rats. In the normal rats, the individual's sensitivity in some

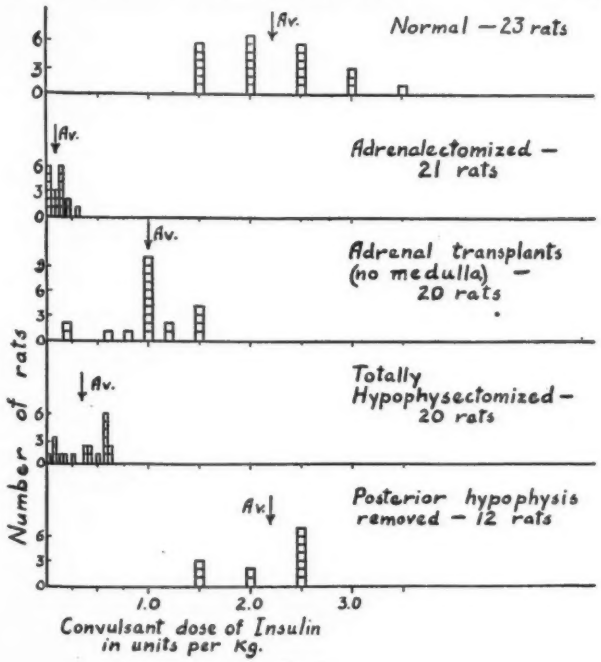

Fig. 1

cases varied; that is, at times a given quantity of insulin would cause convulsions whereas at other times the same amount would not. This variation was, however, within rather narrow limits; i.e., within 0.5 U per kg. Four of 25 rats showed this variation. Also in 2 of the 25 animals tested, no convulsions were produced in many trials, using quantities of from 1 to 6 U per kg.

Twenty-three normal rats were, as figure 1 shows, found to have an average convulsant dose of insulin of 2.2 U per kg.

B). Adrenalectomized rats. After total addrenalectomy, as proved by death within a week following the withdrawal of the sustaining therapy, the convulsant dose was found to average 0.09 U per kg. This sensitivity does not change with the lapse of time, as will be shown to occur in the case of rats with adrenal transplants. Six rats, which had survived total adrenalectomy for 110

days or more, were found to have an average convulsant dose of 0.11 U.

When this very great sensitivity to insulin became clear, it seemed advisable to run further controls. It was found that fasting 12 to 16 hours in the adrenalectomized *healthy* rat was never followed by convulsions; 50 adrenalectomized rats put through an aggregate number of 370 fasts never showed convulsions. It is only the moribund adrenalectomibed rat that occasionally goes into convulsions. Similarly, the injection of water alone into the fasted adrenalec-

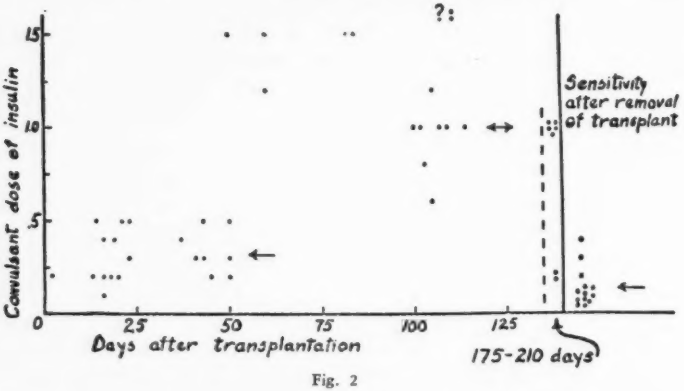

Fig. 2

tomized rat in good condition was found to cause no convulsions.

C). Rats with adrenal transplants. The response to insulin of rats with adrenal transplants was found to change with time. For about 50 days after the operation, the convulsant dose in 22 rats was found to average 0.32 U per kg. Then the sensitivity changed, so that at 100 days after the operation the sensitivity became less. The average convulsant dose of the group was then 1.0 U per kg. These results are shown in figures 1 and 2. No further change with time was noted, a group of 7 rats when measured at 175 to 210 days after operation, showing an average sensitivity of 1 U.

When the transplant was removed, the rats were kept alive in good health by means of the life-sustaining therapy, for at least a week, while they were being retested for insulin sensitivity. Then in turn the therapy was withdrawn from these rats; all died within a week. The operation was followed at once by an increase in insulin sensitivity to a level comparable with that of totally adrenalectomized rats, as figure 2 shows. Histological examination of the transplants confirmed the general finding that only cortical tissue is present in a transplant.

D). Totally hypophysectomized rats. The convulsant dose of insulin in hypophysectomized rats was found to average 0.35 U per kg. in a group of 20 rats. It was found that the more cachectic the rat the greater the sensitivity to insulin. Soon after operation, the convulsant dose was about ½ U, but then as the rats became cachectic this dose decreased. Both cachectic and reasonably healthy hypophysectomized rats are included in figure 1.

E). Rats with posterior hypophysis removed. Twelve of these rats average, as convulsant dose, 2.2 U per kg., a figure the same as that of the normal

rats. No convulsant dose was found for one rat. These results are shown in figure 1.

DISCUSSION

That the adrenalectomized rat is very sensitive to insulin is entirely clear. To produce convulsions in them, only 1/24 the quantity used for the same reaction in normal animals is required. As commonly phrased, adrenalectomized rats have here been found to be "twenty-four times more sensitive to insulin" than the normal. This sensitivity occurs in animals in good condition and by no means moribund.

The general opinion that adrenalin antagonizes insulin has also been confirmed, since animals with no adrenal medulla are convulsed by about one-half the dose of insulin required in the normal. The phenomenon of recovery of some of the resistance to insulin may throw some light on other attempts to show the participation of the adrenal medulla in other detoxifying processes, as have been reported by Wyman (29) and Ingle (30). It is worth noting that no such recovery occurs, apparently, in cats with denervated adrenals over periods running up to 5 months (8).

A rough measurement of the relative importance of medulla and cortex in antagonizing insulin is implied in these data. Since removal of the medulla alone increases the insulin sensitivity only twice, whereas removal of both parts of the adrenals increases it 24 times, the cortex appears far more intimately involved in the antagonism than the medulla. This is in confirmation of much experimental work and many hypotheses (31 and 32).

The convulsant dose of insulin in rats with the posterior hypophysis removed was the same as that of normal rats, indicating, in confirmation of the experiments of Pencharz, Cori, and Russell (23), that the anterior lobe of the pituitary complex, and not the posterior lobe, is the important antagonist to insulin.

SUMMARY

The smallest dose of insulin causing convulsions in normal rats averaged 2.2 U kg.; that in adrenalectomized rats, sustained in good health, averaged 0.09 U; that in hypophysectomized rats averaged 0.35 U, and that in rats with the posterior hypophysis removed averaged 2.2 U.

The convulsant dose of insulin in rats with adrenal transplants, in which no medullary tissue existed was found to change with time. For about 50 days after transplantation, the convulsant dose averaged 0.32 U per kg. Subsequently, the convulsant dose rose to 1.0 U, and it did not change from this level over periods running up to 7 months.

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RESTROPIC EFFECTS OF ANTERIOR LOBE EXTRACTS

CORNELIA WETZLER-LIGETI AND BERTOLD P. WIESNER
LONDON, ENGLAND

Ever since the existence of the reticulo-endothelial system (R.E.S.) has been recognized, a great volume of experimental and clinical work has been expended on defining its functional relationships. But it is a curious fact that the relation between glands with internal secretion and the R.E.S. has not been examined systematically, although various authors have actually attributed endocrine functions to the system itself and have employed, for experimental and therapeutical purposes, extracts prepared from centers of the system. The present communication is concerned with the results of experiments on the influence of pituitary extracts upon the R.E.S.

In view of the controlling position this gland exercises in the endocrine system, extracts from the anterior lobe were used in this first approach. It seemed likely that endocrine factors influencing the R.E.S. would manifest themselves under the influence of pituitary extracts even if any pituitary control were but indirect.

An additional reason for testing pituitary extracts may be mentioned. In experiments not germane to the present issue, it was noted that hypophysectomized male rats showed lowered resistance to infections endemic in the stock used (rat pneumonia, middle ear infections, etc.) and even developed what seemed to be spontaneous Bartonellemia. Administration of alcaline extracts of the anterior pituitary resulted in increased resistance, and it seemed not impossible that this effect was due to a re-activation of the R.E.S.

METHODS

The experiments were carried out on rabbits. Most of the animals were virgins (cross-bred Belgians, body weight 1500-200 gm.). In a few cases, adult females in which pseudo or true pregnancy could be ruled out were employed. The preliminary testing of extracts was carried out in mice, rats or guinea pigs, according to the test required.

The decisive point in experimental procedure concerned the manner in which the activity of the R.E.S. was to be assessed. The methods usually employed are based either on immunological reactions, or on the histological examination of centers of the R.E.S., or on the determination of the rate at which colloidal dyes, injected for the purpose, disappear from the circulation. The latter method was chosen for the present investigation, the 'Congo-red test' being used throughout. This test was designed by Adler and Reimann (1); Stern and Willheim (2) introduced a useful modification which was utilized in the present experiments.

The following procedure was observed. Before any treatment was instituted, a preliminary Congo-red test was undertaken which, briefly, consists of 4 steps. A small volume of blood is withdrawn from an ear vein (sample *A*). A standard volume (2 cc. per 1000 gm. body weight) of a freshly prepared 1 per cent Congo-red solution is then injected intravenously. A second sample (*B*) of blood is withdrawn 6 minutes after the injection of the dye. A third sample (*C*) is taken 60 minutes after the injection. A known quantity of the dye is added to sample *A*. This sample then serves as standard, against which the concentration of the dye in samples *B* and *C*, respectively, is determined colorimetrically. Thus, two values are calculated, referring to *B* and *C* respectively. The difference (*B* — *C*), expressed in percentage of the value of *B*, measures the rate at which the dye has disappeared from the circulation. This percentage value will be referred to as the Congo-red index (C.R. index). Details of the method will be found in the publication cited above (2).

When the initial C.R. index had thus been determined, the experiment proper was undertaken. It consisted in the administration of various extracts and repetition, at regular intervals, of the C.R. test. Thus a series of C.R. indices was obtained for each animal.

Three types of extracts were employed. *A*, Purified extracts with slight gonadotropic activity, prepared by double extraction of anterior lobes. *B*, Gonadotropic extracts. *C*, Extracts with pronounced thyrotropic, and some gonadotropic, activity.

A) Extract 117

This extract was prepared by a modification of known methods (3, 4). Pituitary glands of cattle are removed, and iced immediately after killing. The anterior lobes are ground finely, and 100 cc. of N/10 NaOH or 5 per cent ammonia are added per 50 gm. of glandular substance. The mixture is stirred for at least 1 hour, and then allowed to stand overnight at 4°C. It is then adjusted to pH 6.5 with acetic acid and centrifuged. The supernatant liquid ('*A*') is stored at low temperature, while the precipitate is extracted in a mechanical stirrer with dilute acetic acid (3 per cent) for several hours. After centrifuging, the supernatant liquid is combined with extract '*A*'. The combined extracts are concentrated in a waterbath (45° to 50°C) under reduced pressure. An equal volume of 96 per cent alcohol is added to the concentrate and the precipitate, which forms slowly, is removed by centrifugation. The supernatant liquid is mixed with an equal volume of 90 per cent alcohol and yields, after standing for several hours at low temperature, a voluminous precipitate. This is taken up in water and adjusted to pH 10. The insoluble matter is removed by centrifugation; fractional alcohol precipitation, after acidulation, is repeated and the precipitate obtained, with an alcohol concentration of 70 per cent, is taken up in Evans solution (4 cc. of extract = 1 gm. fresh anterior lobe). The solution is passed through a sterile Seitz filter, and filled in ampoules. These are stored at 4°C.

General properties of E.117. This extract contains only small quantities of gonadotropic hormones if prepared from cattle pituitaries. Slight thyreotropic activity was present in 2 of 5 batches examined on previous occasions.

The extract has no sensible effect on the growth rate of mature female rats. Its effect on the adrenals is doubtful.

Of the 7 rabbits to which this extract was administered, 2 cases will illustrate the effect. In *rabbit 9* (fig. 1) on the first day, the C.R. index was determined as being 43.2. A blood count was also made. Immediately afterwards 1 cc. of E.117 was injected subcutaneously, and the same dose administered in subsequent days. Details will be found in figure 1, which also shows the results of subsequent tests. It will be

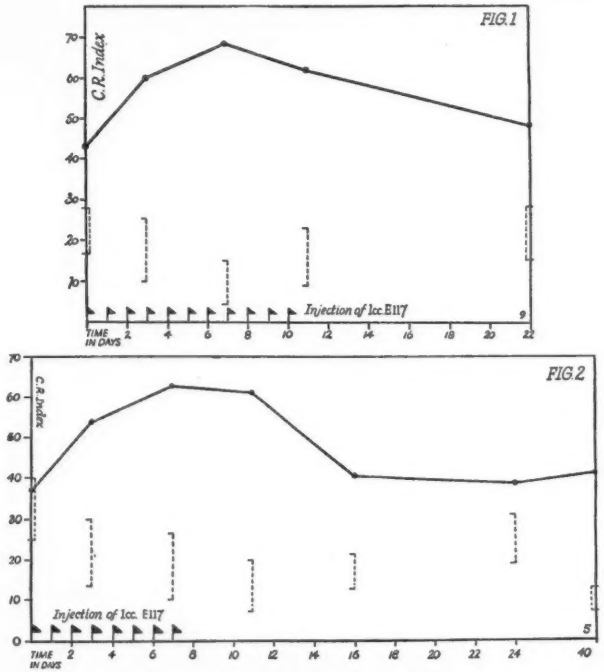

Fig. 1. Effect ot extract 117 upon the C.R. index (*rabbit 9*). The graph shows changes in the C.R. index (unbroken line) and also demonstrates the actual concentration of the dye in the blood 6 and 60 minutes respectively after the injection of the dye (broken vertical lines). The ordinate, read with reference to the index, shows the actual values of the index at each determination; read with reference to the broken vertical lines (absolute values of concentration of dye) it indicates mg. per cent. Thus it will be seen that on day O the concentration of Congo red in the blood was 27.8 mg. per cent, but fell to 15.6 mg. per cent within 54 minutes. The corresponding index, on day O was 43, and one injection of 1 cc. was administered on that day.

Fig. 2. Effect of extract 117 upon the C.R. index, (*rabbit 5*).

seen that the C.R. index rose from its initial level of 43 to a maximum of 71.5, an increase of 65 per cent. Nothwithstanding the continued administration of the extract, the index fell again, and this trend became more marked when the injections ceased. Ultimately, the index returned to its original level. In the course of the experiment, the blood count showed an increase in the number of monocytes from 4 per cent to 7 per cent, whereas the total leucocyte count did not change.

Rabbit 5 (fig. 2) and 2 other rabbits, in which the same experimental procedure was observed, behaved in similar fashion. Although the initial magnitude of the index and its maximum level varied to some degree, the relative rise was of about the same order.

The experiments seemed to indicate that even continued injections would not maintain the rise of the index. But it appeared possible that the ultimate fall of the index was due, not to a lowered reactivity of the R.E.S., but rather to a loss of potency of the extract. The extracts were prepared before the experiment was undertaken and, although stored at a low temperature, they might have lost activity, similar behavior being well known in the case of gonadotropic hormone. This interpretation is supported, though not proven, by two additional experiments.

Rabbit 7 (fig. 3). A batch of extract, prepared about 1 week before the beginning of this experiment, was used. A definite rise in the index was observed, but this ceased after some days. A freshly prepared batch of extract was used immediately afterwards, and a renewed sharp rise occurred. The rabbit died 5 days after the last determination; at the autopsy, the ovary was found to be lacking in either corpora lutea or ripe follicles, but was somewhat hyperaemic. The uterus was in estrous condition, the spleen was small.

Rabbit 12. This animal was subjected to treatment with a batch of E.117, which had previously produced pronounced effects in 3 rabbits. The extract was stored in solution for 3 weeks at 4°C., before being used in the present animal. The initial index was 51; after 3 injections it was 50. One week later the index was found to be 56.

If E.117 is boiled it loses its activity. Thus a batch of E.117, which had proved to be active, was brought to the boiling point for 2 or 3 seconds. Daily injections of 1 cc. each were administered to *rabbit 11* with an initial index of 45.8. After 3 days, an index of 46.8 was found. Injections were continued, but 5 days later the index was still unchanged (45.7).

E.117 is a fairly satisfactory extract. It does not contain any protein, it has no toxic effects, and it is highly active. But attempts at further purification seemed of interest. One of the methods used for this purpose yielded extract 207.

Extract 207. Fresh anterior lobes (cattle) are finely minced and extracted in a Soxhlet. The apparatus is worked under reduced pressure in a water bath (40° to 50°). Distilled water is used as the extracting agent. At the beginning of extraction a few drops of weak ammonia are added to the gland material, and this addition is repeated twice during the first hour of extraction. A current of air is passed through the flask by means of a capillary. With these provisions a very complete extraction is possible, little active substance is lost, and the process is simplified compared with the usual methods employing stirring and centrifuging. The extraction is allowed to continue for 3 hours, and the resulting extract, *A*, is stored in the cold, while a second extraction proceeds. Distilled water is used again, but dilute acetic acid is added whenever necessary to the pituitary material, so that an acid reaction is maintained. This step yields the second extract, *B*. Extract *A* is brought to pH 6.5 with acetic acid and centrifuged. Alcohol is added until a concentration of 50 per cent is reached. The resulting precipitate is discarded. Extract *B* is adjusted to pH 6.5, centrifuged, and then also treated with alcohol, the precipitate being discarded. The two extracts are then combined and brought to an alcohol concentration of 70 per cent. The precipitate which is allowed to form

in the cold is taken up in distilled water and adjusted to neutrality. The suspension is centrifuged and the precipitate discarded. Fractional alcohol-precipitation is carried out after acidulation. The precipitate forming at an alcohol concentration of 60 per cent is discarded, and the precipitate obtained at 70 per cent collected. It is taken up in water, and fractional precipitation is repeated twice after removal of insoluble matter. The precipitate obtained is dissolved, insoluble matter is removed and precipitation with acetone is carried out. The final precipitate is dried with ether. The yield was 0.8 mg. dry substance per gm. fresh anterior lobe. An 0.1 per cent solution in saline was prepared from the dry substance. The solution was tested in immature mice. Daily doses of 0.1 mg. each, repeated on 3 successive days, failed to produce any gonadotropic effects. Thyreotropic activity was not investigated. It may be added that the solution did not yield precipitates with sulphosalicylic acid, but a precipitate was formed with phosphotungstic acid.

The extract was highly active with respect to the C. R. index. Details of an experiment are presented in figure 4. The experiment is of interest, since the method of preparation yielded a substance active in small amounts yet devoid of gonadotropic activity in relatively large doses.

B) Gonadotropic Hormones

The effect of gonadotropic hormones upon the C.R. index is of interest. However, the task of establishing their action is difficult. It is an easy matter to prepare gonadotropic extracts from the pituitary, but it is questionable whether any known method yields purely gonadotropic substances; other effects are usually produced even by purified extracts. The gonadotropic substances obtainable from the blood and urine of some menopausal women do not as a rule affect either the thyroid or the adrenals or the growth rate. These gonadotropic hormones, in all likelihood derived from the anterior lobe, may therefore be chosen where gonadotropic pituitary action is to be investigated.

Extract 208. This extract was prepared from the blood of a woman aged 51 years. The subject excreted large quantities of gonadotropic hormone of the menopausal type. The extract was prepared from 30 cc. venous blood by deproteinization and alcohol precipitation (5). The equivalent of 2 cc. of blood was sufficient to produce weak but definite gonadotropic effects in an immature mouse.

Since the available amount of extract was limited, one rabbit only (*15*) was used for the testing of this extract, receiving one injection daily for 3 successive days. The index fell from 56 to 44. Continuation of the injections was followed by a return of the index to 52.

Extract 193B. This extract consisted of a mixture of 3 different extracts: *a)* gonadotropic hormone prepared from pregnancy urine by a method published previously (6, 7), 1 mg. of the substance containing at least 5 M.U. as defined previously; *b)* similar hormone obtained from human placenta by the sulpho-salicylic-acid-alcohol method (5), and *c)* a gonadotropic extract of anterior lobe of sheep pituitary. This extract was prepared by extraction of the acetone dried gland with alcohol containing 5 per cent ammonia. The extract was purified by repeated fractionated precipitation with acid alcohol.

The anterior lobe extract was actually prepared in 1936 and stored in dry form. It showed high solubility, strong gonadotropic activity, but doubtful thyrotropic activity when tested after preparation. Tested again shortly before the present experiments were undertaken, a slight decrease in gonadotropic activity was noted.

The 3 extracts, all stored in powder form, were mixed in the proportion

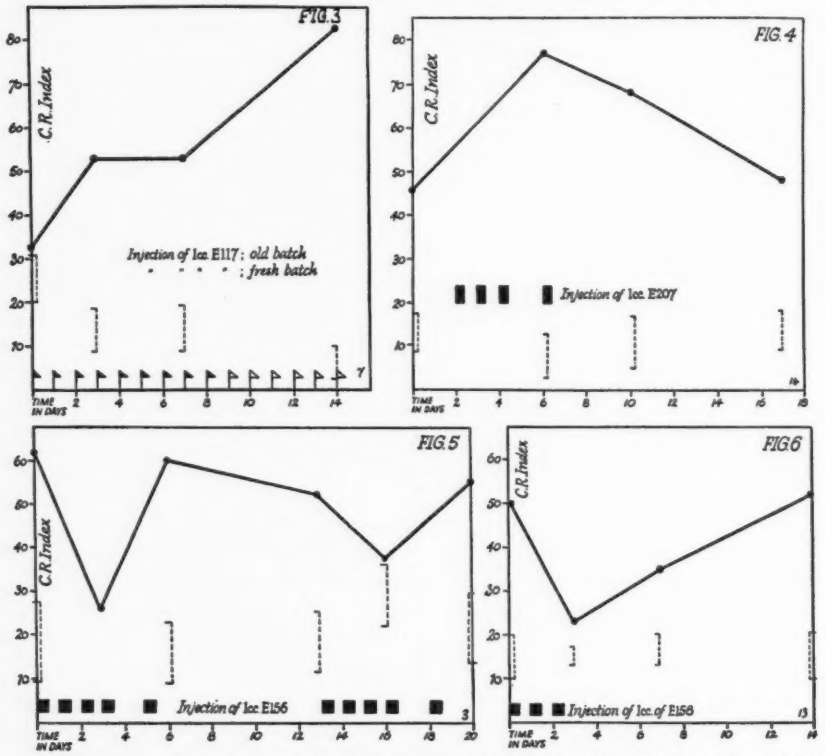

Fig. 3. Effect of extract 117 upon the C.R. index (*rabbit* 7). For explanations see figure 1 and text. Solid flags indicate injection of old batch and clear flags the injection of fresh batch of E.117.
Fig. 4. Effect of extract 207 upon the C.R. index (*rabbit 14*).
Fig. 5. Effect of thyrotropic extract upon the C.R. index (*rabbit* 3).
Fig. 6. Effect of thyrotropic extract upon the C.R. index (*rabbit 13*).

5 (urine extract) : 3 (A.L.P.) : 2 (placental extract). The mixture was strongly gonadotropic, a total dose of 0.2 mg. producing full estrogenic reactions in immature mice.

The extract failed to affect the C.R. index significantly. Thus, *rabbit 2* received 2 injections of 5 mg. each. The index rose from 20 to 26. Injections were continued for 4 more days, and the animal died one day after the sixth injection. A pronounced ovarian effect was noted; the spleen was small, weighing 0.25 gm.

Considering the results as a whole, it would seem that strongly gonadotropic extracts do not necessarily produce any definite effect upon the

C.R. index. An insignificant rise may occur, or else the index may tend to decline. No general and definite effect can thus be reported at the present moment.

C) Thyrotropic Extract

The material used in the present experiments (E.156) was obtained by extraction of dried and defatted glands with trichloracetic acid followed by concentration of the extract under reduced pressure and fractional precipitation. The batch used was prepared in 1936. It was standardized against a very active commercial preparation (Ambinon) which, however, contains a large proportion of gonadotropic hormone. One cc. of Ambinon is stated to contain 150 U of thyrotropic hormone per cc. 2.5 cc. of E.156 corresponded to 2 cc. Ambinon, but the assay of E.156 was only approximate. The extract was used, for the present purpose, in 1937, and stored at 0°C. during the intervening period, so that some degree of potency may have been lost. It contained gonadotropic hormone as seen in tests on immature rats. 0.1 cc. administered in 2 equal doses on 2 successive days produced strong estrogenic effects. The extract did not promote growth when tested for 9 days in 2 female rats.

Thyrotropic extract was used in 3 experiments. The animals did not show any general adverse effects beyond developing temporary symptoms of hyperthyroidism. The influence on the index was very marked, and uniform in the 3 experiments. Details will be found in figure 5 and 6. The essential feature of the experiment is the pronounced fall in the index. The percentage of dye eliminated within the test period fell to about one-half of its original measure. But this fall, like other effects of the extract (activation of the thyroid) is purely temporary. Thus it will be seen, in the case of *rabbit* 3 (fig. 5), that the index tended to return to the norm, notwithstanding continued administration of the extract. The similarity between the behavior of the thyroid and the R.E.S., respectively, suggests that thyrotropic extracts may affect the R.E.S. via the thyroid.

DISCUSSION

In the present study attention is centered on the changes in the Congo-red index. A number of authors (8, 9, 10) have employed this method in the rabbit for the assessment of the functional state of the R.E.S.

The method has also been used in human subjects for the same purpose (1, 8). On the other hand, several authors (11, 12, 13) doubted the value of the C.R. index as a measure of the activity of the R.E.S. Stern and Willheim (2) have carefully considered these objections. They repeated experiments carried out by Moncorps and Gunther (14), and found in agreement with these authors that an experimental damage of the R.E.S. is reflected by a fall in the C.R. index.

Considering the evidence as a whole, it can hardly be assumed that the C.R. index reflects the total functional condition of the R.E.S. Nor can it be denied that it yields a measure of at least one particular aspect of the activity of the R.E.S. Hence the changes in the index observed in the present experi-

ments may be regarded as expressing variations in the functional condition of the R.E.S. of the animals.

In regarding the absolute values of the index, it has to be considered that individual variation is pronounced. At the beginning of the experiment, i.e., before any treatment was instituted, values varying from 20 to 60 were established. In most cases the initial index was of the order 40 to 50, and seems to depend on the age of the animal. In the animals studied by Stern and Willheim the index varied, in untreated animals, from 29 to 43. But it should be remembered that they used older and heavier animals than the present writers.

The variation in the level of initial R.E.S. activity is of lesser importance than it might seem to be, for the changes in the C.R. index in untreated animals amount to but 5 per cent of the initial value. Similarly, inactive extracts produce slight variations only, the initial level being maintained. On the other hand, changes after administration of certain extracts are so pronounced as to leave no doubt about their significance.

Taking the results as a whole, 3 different types of results must be distinguished. The grouping of the results is facilitated by the uniform response of animals treated with any given extract. *a)* Certain anterior lobe extracts, which have but slight gonadotropic activity (in the doses used), produce a pronounced and rapid rise in the activity of the R.E.S. *b)* Other extracts, also prepared from the anterior lobe and endowed with thyrotropic activity, produce the opposite effect, lowering the activity of the R.E.S. *c)* Gonadotropic extracts, whether they be derived from the anterior lobe and/or other sources, cause only a slight fall or rise of the index, and it is doubtful whether these changes are significant.

We are forced to the conclusion that the anterior lobe of cattle pituitary contains a substance which affects positively the activity of the R.E.S. In accordance with a terminology introduced by one of the present writers, and now generally accepted, we propose to refer to this substance affecting the R.E.S. as the 'res-tropic' factor.

The present findings indicate, however, a more complex situation than is the case with respect to some other pituitary secretions, since two contradistinct effects were observed: certain extracts increase, others decrease, the activity of the R.E.S. In other words, pituitary substance yields at least two active derivatives: one which is positively, and another one which is negatively, restropic.

Little can be stated, as yet, of the nature of positive restropin. It is certainly not identical with gonadotropic hormones. The gonadotropic activity of positively restropic extracts was extremely weak; conversely, certain gonadotropic extracts did not definitely affect the R.E.S. Again, although the thyrotropic extract used in the present experiments contained gonadotropic hormone it lowered the index. Nor is the restropic factor identical with the growth factor, which is present in crude ammonia extracts but is lost in the course of preparation of E.117 and E.207. It is manifestly not identical with the thyrotropic factors of the R.E.S., although, of course, quantitative factors may be involved.

Only a few of the chemical properties of the positive restropic factor can as yet be stated. It was present in extracts which did not yield any precipitate

with sulphosalicylic acid; it is destroyed by boiling for a short period; it resists exposure for several hours to temperatures of about 50°C. It is precipitated quantitatively from acid alcohol at concentrations exceeding 70 per cent. Other volatile media also precipitate it from acid aqueous solutions. It is soluble in 95 per cent alcohol containing 3 per cent ammonia. When phosphotungstic acid is added to acid aqueous solutions, a heavy precipitate forms immediately, and the supernatant liquid no longer yields a precipitate on addition of alcohol or acetone; hence the positively restropic factor, like other pituitary hormones, seems to form compounds with this agent. Solubility in water is high.

At this point attention may be drawn to a disadvantage of the method observed in the present experiments. As has been mentioned previously, 6 minutes are allowed to elapse between the injection of the dye and the collection of blood-sample *B*. The purpose of this interval is to allow distribution of the dye throughout the circulation. But it seems that the period chosen was too long. If nothing but distribution would take place during the interval, the initial values of the concentration of Congo-red in sample *B* should tend to be more or less constant throughout a sequence of determinations in any given animal. This is indeed the case, save for minor fluctuations, when inactive extracts are administered or when the animal is not interfered with. But in animals receiving extracts which raise the index, the concentration of the dye in sample *B* is lower than would be expected. In other words, in stimulated animals a rapid deposition of the dye takes place which is not fully reflected by the index. In these cases, the index tends to underestimate the actual activity of the extract.

Negatively restropic extracts contained primarily thyrotropic hormone, and the experiments yielded no indication that any other factor was responsible for the effect.

The matter is complicated by the relative impurity of the extracts; hence further experiments are required before the rôle of negatively restropic effects associated with thyrotropic extracts can properly be assessed. The experiments seem to indicate, although they do not prove definitely, that the negatively restropic action of thyrotropin is as passing as its effect upon the thyroid.

In view of previous findings, it is of interest that the rise of the index was not followed by lowered activity of the R.E.S. Although the observations were extended to nearly 6 weeks, no damage to the system manifested itself.

If we assume, in accordance with an accepted mode of thought, that the effects of glandular extracts reflect the function of the gland in question, then it would follow that the R.E.S. is controlled, to some extent, by the anterior lobe of the pituitary. This control would be effective both negatively and positively; the secretions of the adeno-hypophysis would seem to be capable of lowering or raising the level of the activity of the R.E.S.

SUMMARY

The activity of the reticulo-endothelial system (R.E.S.) was determined, at regular intervals, in rabbits which received injections of various pituitary extracts. Certain aqueous extracts were found to increase the functional ac-

tivity of the R.E.S. Methods of preparing these extracts from the anterior lobe of cattle pituitaries are described. Thyrotropic extracts, containing some gonadotropic hormone, lowered the activity of the R.E.S. for a short period of time. Gonadotropic extracts do not seem to affect the activity of the R.E.S. The anterior lobe of the pituitary appears to control the activity of the R.E.S. It yields at least two derivatives; one is positively restropic (i.e. increases the activity of the R.E.S.) whereas the other is negatively restropic.

The Laboratory,
37, Great Cumberland Place
London, W.I.

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CASE REPORTS

PITUITARY EXTRACT IN SIMMONDS'S DISEASE

GEORGE F. DICK AND WILLIAM C. DINE
From the Department of Medicine,
University of Chicago
CHICAGO, ILLINOIS

It is desired to report briefly two cases of hypopituitary syndrome, each of which has been followed for long periods, and had pituitary extract administered over long periods of time, together with an attempt to evaluate clinically the results of such therapy. No attempt will be made to review the voluminous literature; be it sufficient to say that, compared with experimental work, there is a scarcity of data on the clinical application and results of such therapy.

CASE REPORTS

Case 1. A white, single female, aged 17 years, was first seen by Dr. George F. Dick on January 22, 1934. She stated that she had been well until one year previous, at which time her menses ceased, and afterward she began gradually to lose weight (from 103 to 80 lb.). For 6 months prior to admission, she had vomited after meals and had become very tired. Her menses had started at 13 and had been regular and normal until one year previous. The family history was negative. The girl had been better than an average student in school, but during the past year had lost interest in her work.

Physical examination revealed an emaciated girl, looking older than her years, apprehensive, and with a tendency to hysterical laughter. Her blood pressure was 100 systolic, 60 diastolic, pulse 45 and temperature 98.6° F. Physical examination gave negative findings except for delayed dentition, small genitalia, emaciation and a dry skin.

The Wassermann and Kahn tests gave negative findings, the blood and urine were normal. Roentgen examination of the skull revealed a normal sella, and x-ray of the chest, esophagus, stomach and duodenal bulb revealed no abnormalities. X-ray studies of the long bones revealed no abnormal skeletal development.

The B.M.R. was −22 per cent. The patient was put on desiccated thyroid 5 gr. 3 times a day and a high caloric diet with between-meal feedings. On April 27th her condition was unchanged and she had lost 3 lb. more. She was then given 4 ampoules of antuitrin-S at weekly intervals. On May 31st, 1934, the patient's weight was 69 lb. and she was put on phyone (growth factor)[1] 1 cc. daily, which was increased to 2 cc. daily on July 9th, and this was continued until August 1934. There was no change in the patient's condition and no gain in weight.

On August 8, 1934, the patient was re-admitted to the hospital for 3 days. Her B.M.R. at this time was −28 per cent; her red blood count 3.79 million, her serum chloride 90.8 mg. per cent. She was again discharged and given phenolbarbital and bromides without results.

On January 18, 1935, the patient again entered the hospital. Her weight was 69 lb. (a total loss of 34 lb.), she was still vomiting after meals, the amenorrhea had continued, and her pulse was 45 to 50. The B.M.R. was −17 per cent; her R.B.C. 3.6 million; and hemoglobin 76 per cent. On January 25th 1 cc. phyone subcutaneously daily was started, and 8 days later the dosage was increased to 2 cc. Four B.M.R. determinations during this period varied between −29 and −23 per cent. The patient was discharged on phyone, 1 cc. daily. On April 26th, her weight had increased to 79½ lb., she was not vomiting, she had no nausea and her appetite was good. At this time the phyone was discontinued.

On May 11th, her weight had dropped to 74 lb. and nausea, vomiting, anorexia and restlessness had returned. The patient had no further medication until September 8, 1935. Her nausea and vomiting were still present. Phyone therapy was then resumed (1 cc. daily), 10 days later her nausea and vomiting had ceased, and one month later her weight had increased to 80 lb. and she felt much better and had no nausea. On November 25th her B.M.R. was −23 per cent.

On January 14, 1936 the medication was stopped, and on February 3rd her weight had dropped to 80 lb. and the B.M.R. was −23 per cent. No therapy was given until September 28, 1936, at which time she was started on maturity factor,[2] 1 cc. daily. On February 9, 1937 her weight was 94 lb., she was feeling well, was not vomiting and the medication was discontinued.

On July 22, 1937, her weight was 92 lb., she was a normal acting individual, with no vomiting; the only striking thing on physical examination was the large number of fillings in her teeth for a girl of her age. During October 1937, she had a normal menstrual period, and her B.M.R. is now −22 per cent. She is now working as a telephone operator.

Case 2. This patient entered Billings Hospital on March 25, 1936. She was a married 27-year-old white female. For the preceding 6 years she had suffered intermittently from severe frontal headaches 2 to 3 times a week. During the attacks the patient was usually drowsy, and slept part of the time. Often the headaches were accompanied by marked nausea and vomiting. Her menses had started at 12, and were regular and normal until 8 years previous, when she started to menstruate only 2 or 3 times a year, and for the past 3 years there had been a complete amenorrhea. During the past 2 years her teeth had become very carious, and she had noticed a marked tendency to falling of the pubic and axillary hair. She was continually tired, and did her housework with great difficulty. There was a complete loss of libido. No pregnancies had occurred. Eight years previously she had weighed 124 lb.; on admission, she had gradually gone down to 90 lb.

Physical examination revealed a thin, emaciated female looking older than her years. There was almost complete absence of axillary hair, and the pubic hair was scanty. The blood pressure was 104 systolic, 60 diastolic. The heart was small and narrow, and pelvic examination revealed a small uterus. The skin was thin, pale, delicate and faintly wrinkled. Neurological examination was entirely negative. The white blood count was 4,700, red blood count 4.23 million, and the urine was negative. Both Wassermann and Kahn tests showed strongly positive findings. The blood urea was 11.1 mg. per cent, the non-protein nitrogen 29 mg. per cent, blood sugar 73 mg. per cent and cholesterol 138 mg. per cent. Spinal puncture showed no abnormalities. X-ray of the skull revealed a normal sella, and x-rays of the chest and esophagus were normal. X-ray examination of the stomach showed a small diaphragmatic hernia. The visual fields were normal, and further neurological examination by Dr. Percival Bailey revealed no evidence of pituitary tumor. Her B.M.R. at this time was −24 and −38 per cent. A diagnosis of syphilis and of

Simmonds's disease was made, and the patient discharged to the referring physician for anti-luetic therapy. The idea was entertained at this time that there might be a gumma present involving the anterior pituitry.

After 3 months of neo-arsphenamine and bismuth at home, the patient returned to the hospital in May of 1936, and presented a marked exfoliative dermatitis. This cleared up in about a week in the hospital, and on May 22nd she was started on 1 cc. each, daily, of hebin (gonadotropic factor)[1] and phyone (growth factor)[1] and this was continued until June 16, 1936. The B.M.R. at the beginning of the period was −21 (2 determinations), and on June 2, 1936 it was plus 11 per cent; 3 days later it was plus 16 per cent, and on June 11, 1936 plus 13 per cent. On

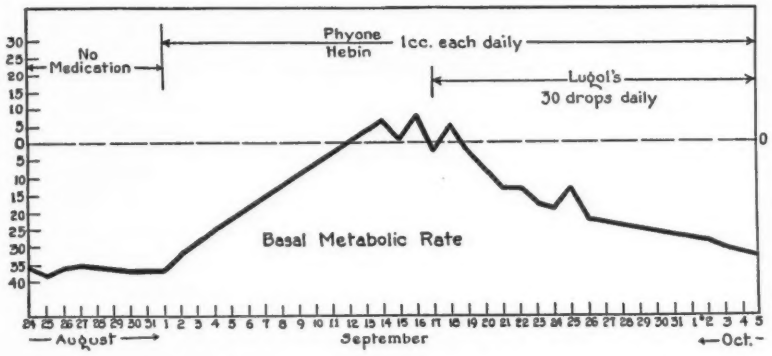

Fig. 1

June 29th, 13 days after stopping the medication it had fallen to −4 per cent, and on July 3rd to −13 per cent. On June 22nd, the patient started to menstruate and flowed quite normally for 4 days, the first time in 4 years. She was discharged on July 10, 1936. Her nausea was gone and the headaches had cleared up. Her Wassermann and Kahn tests were still 4+, and she returned to her physician for anti-luetic therapy.

August 23, 1936 the patient again returned to the hospital. She had had no more menstrual periods, and her weight had dropped from 84 to 75 lb. She suffered from nausea, severe headaches, and vomiting. Five B.M.R. over a period of a week varied between −35 and −38 per cent (fig. 1). On September 1, 1936, she was put on hebin and phyone, 1 cc. of each daily, and this was continued until September 17, 1936. Daily rates were taken, but a few were unsatisfactory because of a low-grade temperature. However, on September 14, 15 and 16th, satisfactory readings were obtained which were, respectively, +7, +1 and +8. During this period her weight dropped from 81.4 lb. to 70 lb., and her pulse ran from 110 to 120. She perspired, her skin was moist, there was nervousness and a tendency to crying spells and she was very uncomfortable.

On September 16, 1936, 3 c.c. daily of Lugol's solution was started, and the hebin and phyone continued. Three days later (September 18th) her rate was +5 per cent, on the 19th −2 per cent, on the 22nd −13 per cent, on the 23rd −28 per cent, and on October 5th −28 per cent. The pulse rate was back to normal, the weight had gone up to 32.7 kg., and the nausea and nervousness had stopped.

On October 5th, Lugol's solution was discontinued and polyansyn[2] 1 cc. daily

[1] Wilson & Co.
[2] Armour & Co.

was substituted for the hebin and phyone. The almost daily B.M.R. during this period varied between −35 and −25 per cent. On October 31st, the dosage was increased to 2 cc. daily, and continued until November 11th, with the B.M.R. still varying between −25 and −35 per cent. The patient felt no better and still had occasional headaches and vomiting spells.

On November 28th, after 2 weeks without any medication, she was given phyone 1 cc. daily, and 5 U insulin before meals (1). It was necessary to discontinue the insulin because a dose as low as 3 or 4 U would produce extreme nervousness, apprehensiveness and crying. A fasting-blood sugar at this time was 58 mg. per cent; 1 hour after 5 U of insulin the blood sugar was 49 mg.; 2 hours 51 mg.; and 3 hours 43 mg. per cent.

The phyone was continued until December 14th without any change in the B.M.R. At this time hebin, 1 cc. daily, was substituted for the phyone and continued until January 18, 1937, the B.M.R. still varying between −25 and −35 per cent. However, the headaches became much less severe, she was up and around the ward and looked much better. On January 18th medication was discontinued for a metabolic balance, and during this period her headaches and vomiting returned and she was very miserable. On February 2, 1937, the phyone and hebin were again started (1 cc. daily) with symptomatic improvement, but the B.M.R. still ran around −34 per cent. During this time almost daily B.M.R. were taken, and anti-luetic therapy was also continued.

She was sent home February 20, 1937 to receive 1 cc. each of hebin and phyone daily. She was again seen in May 1937. She had no headaches or vomiting, and felt well. However, when the extract had run out one month previous, the headaches and vomiting had returned, to disappear only when the dosage was resumed. The B.M.R. was still —32 per cent. Since May 1937, the patient has been receiving Armour's maturity and gonadotropic factor. On discontinuing it, she becomes uncomfortable. On the last admission to the hospital, substitution of other medication unknown to the patient caused a return of the old symptoms. The B.M.R. still runs around −35 per cent, and she now weighs 84 lb. On October 5, 1937, the dosage of gonadotropic was increased to 20 U daily (more concentrated extract) without any change, and on October 22nd the dosage was increased to 40 U daily. In December, 1937, her B.M.R. was −34 per cent, she weighed 86 lb. and was comfortable.

SUMMARY

Two cases of hypo-pituitary syndrome are reported. Both cases seemed to do better with maturity and gonadotropic factor than without it. Such a conclusion may be subject to error, since it is based on clinical judgment only. The first case continues to improve without therapy. It is interesting that, in the second patient, symptoms of hyperthyroidism occurred coincident with a rise in the B.M.R., while on pituitary extract, and that a fall in rate with amelioration of symptoms followed the use of iodine. The failure of a repetition may be due to the antihormonal theory of Collip (2), or it may be that the extracts used later were not as potent in their thyrotropic effect.

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PITUITARY DWARFISM: TREATMENT WITH GROWTH HORMONE

NELSON M. TAYLOR

From the Wayne County Clinic for Child Study

DETROIT, MICHIGAN

Evans and Long (1) first reported, in 1921, the preparation of an anterior pituitary extract which produced gigantism in normal rats and growth in hypophysectomized rats. The first clinical use of growth hormone of the anterior pituitary was reported by Engelbach (2) in 1932. Treatment of human pituitary dwarfism resulted in satisfactory growth. Since then additional reports (3) of treated cases have appeared in the literature. Schaefer (4) reports treatment of 11 cases. In at least 6 of these, growth exceeded the normal increment, and in all it materially exceeded that anticipated on the basis of previous development. Turner (5) detailed his treatment of 9 cases of endocrine growth deficiency. In 5 cases, growth exceeded the average increment. The reason for failure in his other 4 cases is unexplained except by application of Collip's (6) antihormone theory. Shelton et al (7) report treatment of 5 cases. All of these responded with growth both greater than the normal increment and greater than that anticipated on the basis of previous growth.

Engelbach's report of his first treatment case notes the use of massive doses of Evans's growth hormone (a saline suspension of finely ground beef anterior pituitaries), frequently amounting to 9 cc. daily. His later reports are included in the recent summary by Schaefer. The latter frequently uses dosages of 5 cc. of antuitrin-G 3 times weekly. Turner reports the employment of doses ranging from 10 cc. of growth hormone daily, 5 cc. daily, 3 cc. daily, or these dosages every 2 days. Shelton suggests that the institution of massive doses of growth hormone is theoretically imperative. On the basis of rat dosage he states that from 15 to 30 cc. should be administered intraperitoneally daily. However, he has actually used 13 cc. daily in the gluteal muscles, and regularly employs 5 cc. of growth hormone 6 days a week in human treatment.

METHODS

We are presenting 8 cases of pituitary dwarfism studied in the Wayne County Clinic for Child Study.[1] Method of examination and establishment of the diagnosis of pituitary dwarfism has been outlined before (8). Treatment in each case was started with the immediate use of 2 cc. or (in one case) 3 cc. of anterior pituitary growth hormone (antuitrin-G) 3 times weekly. In only one case was the dosage increased, and in that one even 5 cc. 3 times weekly was unsuccessful in materially accelerating growth.

As Schaefer has established, the employment of thyroid extract is frequent-

[1] The director of the Clinic is Mrs. Geneva M. Ellwood. The Clinic is operated under the supervision of the Wayne County Juvenile Court. The presiding Judge is Hon. D. J. Healy, Jr.

ly beneficial when used in conjunction with growth hormone. Furthermore, it appears to be specifically indicated when there is roentgenographic evidence of delayed osseous development or a depressed basal metabolic rate. Thyroid extract[2] is given to the point of individual tolerance, starting with 1 gr. daily and increasing the dosage until a maximum has been reached. This is determined by close observation of temperature, pulse and weight at weekly intervals, with occasional determinations of the B.M.R.

Seven of the 8 cases were referred to the Clinic because of serious behavior difficulties, and an exhaustive study of these difficulties was made in each instance. None of the children was placed in a so-called reform institution, but all have been under the supervision of a Clinic worker. At the termination of the treatment period, a summary of behavior of each patient was compiled from information received at home, at school, from Clinic records and from other interested agencies.

CASE HISTORIES

Case E-458. A male, aged 8 years 7 months, of American-English-Scotch extraction, was diagnosed as having hypothyropituitarism. This was a full-term pregnancy, instrumental delivery. The patient weighed 7.7 lb. at birth, had rachitis at 8 months, teethed at 1 year, walked at 13 months, but did not talk until 3 years old. He was bottle-fed 9 months. The patient has had severe pertussis; also chickenpox and parotitis. Tuberculin tests have repeatedly been negative, and chest x-ray showed normal findings. The mother was short and overweight, a sister, six years old, was of an average size.

The patient's delinquency was larceny. He had low average general intelligence, average social judgment, high average planning capacity, and very superior manipulative ability.

Physical Examination. The patient was a proportionately developed, undersized boy who appeared to be about 2 years younger than his stated age. There was a mild vasomotor instability with a slight telangiectasis of the anterior chest, and a mild chronic hypertrophic rhinitis. Rachitic rosary and Harrison's Groove were present.

Laboratory Examinations. Roentgenographic study for osseous development revealed a 5-year delay in osseous development (films showed striations suggestive of healed rachitis). The B.M.R. was —13 per cent.

Treatment. The patient had no treatment for a period of 2 years 7 months following the original examination, during which time the growth increment was 4.1 inches, which was 1 inch less than average. At the age of 11 years 2 months, treatment with growth hormone (antuitrin-G, 2 cc. 3 times weekly) together with thyroid extract to a tolerance of 9 gr. daily was instituted. At the original examination, patient's height was 1.8 inches below the minimal normal. At the time of the onset of treatment, his height was 2.3 inches below the minimal normal. Treatment has been continuous for 1 year and 9 months. His height now is 0.9 inches below the minimal normal.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	60.0 lb.	63.0 lb.	73.5 lb.	75.9 lb.
Height	51.0 in.	53.3 in.	56.0 in.	56.9 in.
Basal Metabolic Rate	−13%			−11%
Osseous Development ...	5 yr. delay			3 yr. delay
Epiphyseal Closure				2 yr. delay

[2] Thyroid emplets of Parke, Davis & Co.

Behavior. The patient is reported to be making a satisfactory adjustment. There has been no repetition of his delinquency. The school states that he is more stable, more coöperative, and the grading of his academic work is satisfactory.

Case E-590. A male, aged 15 years 2 months, of American-Dutch-German extraction, was diagnosed as having hypopituitarism. His birthweight was 6.5 lb. He cut his first tooth at 14 months, walked at 20 months, but did not talk until after 2 years. He had measles at 6 years, chickenpox at 7 years. He has worn glasses since the age of 5. The patient's paternal grandfather was short, his mother short and overweight, and one brother, 16, had normal development.

There was no delinquency in this case, the patient having been referred because of excessive fears on a sexual basis. He had borderline-defective general intelligence, borderline-defective social judgment, average planning capacity, and average manipulative ability.

Physical Examination. Complete examination could not at first be accomplished because of the patient's extreme conflicts due to retarded sexual and somatic development. He was extremely withdrawn, and had apparently very marked feelings of guilt, which were superimposed upon a customary sensitiveness and timidity. He was definitely undersized, with essentially proportionate measurements. The skin was extremely dry, and there was a marked vasomotor instability with dermographia. He had poorly corrected defective vision. There was a marked crowding of the upper anterior teeth with malposition of the upper cuspids. The genitalia were markedly immature, the testes small but of normal consistency and well descended. The penis was small, the prepuce markedly redundant and phimotic.

Laboratory Examination. Roentgenographic study for osseous development revealed a delay of between 1 and 2 years in epiphyseal closure. The B.M.R. was —3 per cent.

Treatment. Growth hormone (antuitrin-G, 2 cc. 3 times weekly) was instituted at 15 years 9 months, together with thyroid extract to a tolerance of 10 gr. daily. This continued for 2 years. His height before the onset of treatment was 2.6 inches below the minimal normal for his age. It is now 0.4 inch above the minimal normal in relation to age. The weight increase has been proportionate.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	94.4 lb.	96.0 lb.	118.0 lb.	106.8 lb.
Height	58.8 in.	61.4 in.	64.5 in.	64.1 in.
Basal Metabolic Rate	−3%			−18%
Epiphyseal closure	2 yr. delay			1 yr. delay

Behavior. A rather dramatic change has occurred in this patient, as attested by his parents and Clinic worker. From an extremely shy, shut-in personality, the boy has become less sensitive and more aggressive. His school work is satisfactory.

Case E-596. A male aged 15 years 9 months, of American-English-Scotch-Irish extraction, was diagnosed as having hypopituitarothyroidism. The patient's birthweight was 9.0 lb. Dentition began at 11 months, walking at 13 months, talking at about 2 years. He has had severe scarlet fever at 3½ years, measles and bronchopneumonia at 7, otitis media following measles, and chickenpox at 8 years. The mother was 5 feet 10 inches tall and weighed 140 lb.; the father 5 feet 10 inches tall and weighed 160 lb. All maternal and paternal uncles were tall, some over 6 feet, with the exception of a paternal uncle who was 5 feet 6 inches. Two younger sisters were both 'large for their age.'

There was no delinquency. The patient had a good school record. (Psychometric studies were not done.)

Physical Examination. The patient's statural size was approximately that of a boy 1 year younger than stated age, with measurements essentially proportionate. He had slightly defective right vision and slightly retarded genital development; a small amount of pubic hair, but no other secondary sex characteristics. The testes were rather small and soft.

Laboratory Examinations. Roentgenographic study for osseous development revealed a delay of 1 to 2 years in osseous development.

Treatment. The patient received growth hormone (antuitrin-G, 2 cc. 3 times weekly) without additional thyroid medication for 26 months. At the onset of treatment, his height was 1.4 inches below the minimal normal, at termination of treatment 2 inches above the minimal normal, and 2.5 inches below the maximal normal.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	98.5 lb.	91.6 lb.	133.6 lb.	109.8 lb.
Height	60.0 in.	61.4 in.	66.3 in.	64.3 in.
Osseous Development	2 yr. delay			

Behavior. This patient did not present a behavior problem.

Case E-720. A male aged 11 years 6 months, of American extraction, was diagnosed as one of hypopituitarothyroidism. He weighed 6.5 lb. at birth; this was a full-term pregnancy with normal delivery. The patient was bottle-fed and offered no feeding problem. He walked at 2 years, talked at 1 year, and toilet habits were established at 2 years. There were mild cases of measles at 4, parotitis at 8, and recently the patient has had a mild attack of scarlet fever. At 8 years of age, he was run over by an automobile, sustaining a fractured jaw and fractured skull; there were apparently no sequellae. The mother deserted the patient (an only child) at 6 months. The father is small and thin. The delinquency charge was larceny and incorrigibility. The patient had low average general intelligence, low average social judgment, high average planning capacity, and superior manipulative ability.

Physical Examination. The patient was approximately the size of a boy 1 year younger. He had the general appearance of malnutrition, except for a prominent abdomen. There was a broad forehead with rather prominent frontal bossae. The tonsils were markedly hypertrophic and injected. Moderate rachitic rosary and small umbilical hernia were also found. The scrotum and testes were small, the latter soft, and when the patient was in the prone position they retracted toward the external inguinal ring. The prepuce was redundant, adherent, and phimotic. There was a slightly accentuated lumbar lordosis. The tibiae evidenced a slightly increased lateral bowing.

Laboratory Examinations. Roentgenographic study for osseous development revealed delay of approximately 1 year in osseous development. The B.M.R. was +3 per cent.

Treatment. Growth hormone (antuitrin-G, 2 cc. 3 times weekly) together with thyroid extract to a tolerance of 7 gr. daily was instituted. At the onset of treatment, the patient's height was 1.8 inches below the minimal normal, after continuous treatment for 2 years, it is equal to the minimal normal.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	63.2 lb.	66.2 lb.	81.5 lb.	79.3 lb.
Height	52.5 in.	54.3 in.	57.8 in.	57.8 in.
Osseous Development ...	1 yr. delay			Normal
Epiphyseal closure				2 yr. delay
Basal Metabolic Rate	+3%			+13%

Behavior. Reports on this patient indicate that he has evidenced slight improvement in behavior. His school work is satisfactory, but does not approach his ability.

Case E-757. A male aged 12 years 5 months, of American extraction was diagnosed as having hypopituitarothyroidism with early pituitary cachexia. This was a normal pregnancy and delivery. The patient weighed 5.5 lb. at birth, he was breast-fed for 10 months. There was normal dentition, walking, and talking. He had mild cases of parotitis, measles, and whooping cough. The patient's mother was short, his father tall and thin.

His delinquency was repeated school truancy. The patient had low average general intelligence, borderline-defective social judgment, borderline-defective planning capacity, and average manipulative ability.

Physical Examination. The boy was markedly undersized, with a proportionate weight. There was a relative microcephaly. The skin was dry, and over both the upper and lower extremities was a diffuse cyanotic mottling. The hands presented senile characteristics, also true of the facies. There was a moderate chronic tonsillitis and adenoiditis, and marked dental calcium deficiency with multiple caries. The genitalia were markedly immature.

Laboratory Examinations. Roentgenographic studies for osseous development showed a delay of 3 to 4 years. The B.M.R. was –25 per cent.

Treatment. Growth hormone (antuitrin-G, 2 cc. 3 times weekly) together with thyroid extract to a tolerance of 10 gr. daily was instituted. Treatment has been continuous over a period of 1 year and 7 months. At the onset of treatment the patient's height was 4.0 inches below minimal normal; it is now 1.0 inches below minimal normal, exceeding that anticipated on the basis of his previous growth by 3.3 inches.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	63.2 lb.	72.7 lb.	83.5 lb.	81.1 lb.
Height	52.0 in.	56.0 in.	57.6 in.	58.6 in.
Osseous Development	4 yr. delay			Normal
Epiphyseal Closure				2 yr. delay
Basal Metabolic Rate	−25%			+12%

Behavior. A marked improvement in behavior is reported in this patient. He is more obedient, contented and happy. The school teacher has noticed good effort, ambition, and his academic work is satisfactory. The worker has remarked an increased stability and 'less nervousness.' There has been no repetition of the delinquency.

Case E-770. A female aged 15 years 1 month, of American-Italian extraction was diagnosed as having hypopituitarism (early pituitary cachexia). The patient weighed 9.0 lb. at birth. It was a full-term pregnancy and normal delivery. Dentition occurred at 6 months, walking at 14 months, and talking at 1½ years. The patient was easily toilet-trained, and was breast-fed for 2 months, then bottle-fed, with no difficulty in weaning. She suffered a severe infection in the right leg at 4 years, and influenza at 13. There has been chronic enuresis. Menses have not been initiated. Both parents are short and underweight. The patient's delinquency: habitual truant from home and school. She had borderline-defective general intelligence, borderline-defective planning capacity, borderline-defective social judgment, and high average manipulative ability. She was quiet, stolid, and at least as retarded in emotional development as in physical and mental development.

Physical Examination. This patient was a proportionate, undersized girl apparently 4 or 5 years younger than the stated age. Her facies, however, were somewhat more mature than her statural size. She was a normal in miniature. Her skin was

very dry, with a definite telangiectasis on the anterior chest, and a very slight subdermal thickening. There was a moderate sclerosis of both tympanic membranes with bilaterally defective audition. The tonsils were small, moderately infected. There was a moderate dental calcium deficiency with one carious tooth. No secondary sex characteristics were present. She had a small umbilical hernia.

Laboratory Examinations. Roentgenographic study for osseous development revealed delay of approximately 2 years in epiphyseal closure. The B.M.R. was +12 per cent.

Treatment. The patient was placed on growth hormone therapy (antuitrin-G, 3 cc. 3 times weekly) and thyroid extract to tolerance of 11 gr. daily. At the onset of treatment the patient's height was 7.9 inches below the minimal normal; she is now 5.6 inches below the minimal normal. Treatment was given for 1 month, interrupted for 4 months, and then was continuous for a period of 11 months.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	75.7 lb.	95.7 lb.	82.0 lb.	102.5 lb.
Height	52.5 in.	60.4 in.	55.5 in.	61.1 in.
Epiphyseal Closure	2 yr. delay			Normal
Basal Metabolic Rate	+12%			−25%

Behavior. This patient has made an excellent adjustment. She is now described as coöperative, happy and industrious. The school reports good attendance and satisfactory academic grading. The enuresis is entirely corrected.

Case E-797. A male aged 11 years 9 months, of American-Irish-Polish extraction, was diagnosed as having hypopituitarothyroidism. The mother was nauseated during the entire pregnancy, and suffered from severe edema of the lower extremities. This was an instrumental delivery; birth weight 7.5 lb. The patient was small in infancy, and has always been small. He was breast-fed 9 months, walked at 8 months, teethed at 1 year, and talked at 18 months. He has had uncomplicated cases of measles and pertussis, and a comminuted fracture of the left ankle at the age of 9. The father was 5 feet 6 inches tall and slight in build. He was a prize-fighter. The mother was 4 feet 11 inches tall and weighed 155 lb. She weighed 95 lb. at the time of the patient's birth. The maternal grandmother is diabetic, also short, and weighed 200 lb. A maternal cousin was diabetic, short, and weighed over 300 lb. The patient's delinquency: repeated larceny. He had low average general intelligence, very superior social judgment, borderline planning capacity, and average manipulative ability.

Physical Examination. This patient was a markedly undersized boy with proportionate weight and generally proportionate measurements. His size was approximately that of a child 4 years younger.

Laboratory Examinations. Roentgenographic study for osseous development indicated a delay of 1 year. The B.M.R. was −23 per cent.

Treatment. Growth hormone (antuitrin-G) was instituted. For a period of 7 months the patient received 2 cc. 3 times weekly. Because of his poor response, dosage was increased to 5 cc. 3 times weekly, and this has continued over a period of 7 months. Thyroid extract to a tolerance of 5 gr. daily has been given concomitantly. Therapeutic response has been very poor in relation to that obtained in the other cases. Normal increment is 2.2 inches, whereas the actual was 2.3 inches. Efforts to rule out all non-endocrine disease responsible for retarded physical development have failed to reveal a reason for this relatively unsatisfactory response to growth therapy.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	54.2 lb.	66.2 lb.	57.5 lb.	75.9 lb.
Height	48.7 in.	54.7 in.	51.0 in.	56.9 in.
Osseous Development	1 yr. delay			Normal
Epiphyseal Closure				2 yr. delay
Basal Metabolic Rate	−23%			−27%

Behavior. The patient's mother reports that he is considerably 'less nervous' than previously, and that there has been no known repetition of his former delinquency. However, he is frequently truant from home.

Case E-801. A male, aged 12 years, of Canadian-French-English extraction, was diagnosed as having hypopituitarothyroidism. The mother had pneumonia during pregnancy with this patient. There was a breech presentation, delivered as such, and 'dry birth.' The patient weighed 4 lb. at birth, and had broncho-pneumonia at

TABLE 1. ENDOCRINE GROWTH THERAPY

Case	Sex	Age at Onset Treatment		Antuitrin-G 3 times wk.	Thyroid Extract Tolerant Dose per Day	Growth Increment per year		2 yr.
						Minimal Normal	Actual	Actual
		Yr.	Mo.			In.	In.	In.
E-458	M	11	2	2 cc.	9 gr.	1.9	3.0	—
E-590	M	15	9	2 cc.	10 gr.	1.4	2.5	5.7
E-596	M	15	9	2 cc.	—	1.4	2.8	6.0
E-720	M	11	6	2 cc.	7 gr.	1.7	2.5	5.3
E-757	M	12	5	2 cc.	10 gr.	1.8	4.3	—
E-770	F	15	1	3 cc.	11 gr.	0.7	3.0	—
E-797	M	11	9	2 cc. 7 mo. 5 cc.	5 gr.	1.7	1.9	—
E-801	M	12	6	2 cc.	5 gr.	0.9[1]	2.2[1]	—

[1] Six months growth.

6 months. Dentition began at 8 months, walking at 10 months, talking at 18 months. He has had measles and pertussis. The father, mother and one brother were of 'average size.'

The patient's delinquency: larceny, incorrigibility, and truancy. He had average general intelligence, superior social judgment, average planning capacity, and superior manipulative ability.

Physical Examination. The patient's height is approximately that of a boy 1 year younger, with measurements essentially proportionate. He had multiple dental caries and a small umbilical hernia.

Laboratory Examinations. Roentgenographic study of osseous development revealed delay in osseous development and epiphyseal closure of about 2 years. Roentgenogram of skull reveals normal sella turcica. The B.M.R. was +6 per cent.

Treatment. The patient has been under treatment with growth hormone (antuitrin-G, 2 cc. 3 times weekly) with thyroid extract to a tolerance of 5 gr. daily for 8 months. When he was first examined, his height was 1.2 inches below the minimal normal; then followed a period of observation of 6 months. At the onset of treatment his height was 1.3 inches below the minimal normal, and after 8 months of treatment it now exceeds the minimal normal by 0.8 inch.

	Before Treatment		After Treatment	
	Actual	Minimal	Actual	Minimal
Weight	72.0 lb.	69.4 lb.	83.0 lb.	75.9 lb.
Height	54.7 in.	56.0 in.	58.0 in.	57.2 in.
OsseousDevelopment	2 yr. delay			2 yr. delay
Epiphyseal Closure	2 yr. delay			2 yr. delay
Basal Metabolic Rate	+6%			+10%

Behavior. The patient is extremely aggressive, has a very marked leadership ability and is popular with other children, particularly girls. However, his activities are almost totally non-constructive. He is restless, excitable and fails to conform to group management. His general attitude of lawlessness has not improved during the course of treatment, although there has been no truancy and no known theft during this 8-month period.

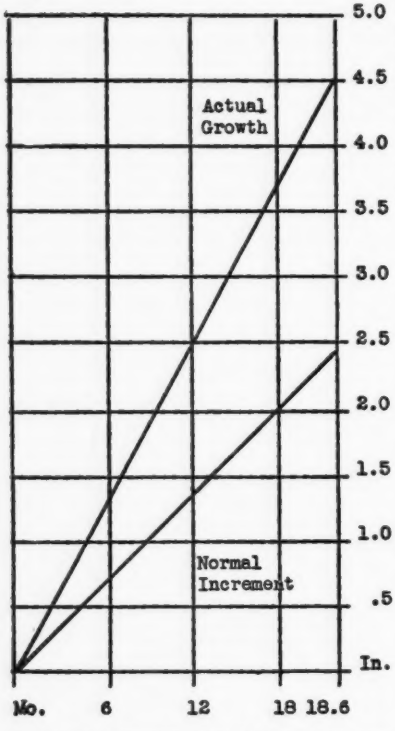

Fig. 1. Composite chart of growth. Average duration of treatment, 18.6 months; average gain in height on treatment, 4.56 inches, average normal increment for age and time, 2.41 inches.

DISCUSSION

Eight cases of physical retardation due to endocrine deficiency are presented. Seven of these were males varying from 11 years 2 months to 15 years 9 months at the onset of treatment. One female was 15 years of age.

All cases received growth hormone therapy in the form of antuitrin-G, and all but 1 received thyroid extract concomitantly. Six cases were treated with 2 cc. of antuitrin-G 3 times weekly. One case (*E-770*) was treated with 3 cc. of this extract 3 times weekly. After a period of 7 months treatment with 2 cc. of antuitrin-G 3 times weekly, 1 case (*E-797*), because of relatively unfavorable therapeutic response, was given 5 cc. 3 times weekly for a similar period. The increased dosage failed to elicit any more marked growth. Despite the fact that this case made the poorest showing of any in the series, his growth at the end of 1 year exceeded the normal increment by 0.2 inch.

Among the 8 cases in which a favorable therapeutic response was elicited, 1 patient grew at the rate of 5 times the presumed increment, 1 trebled, and 3 more than doubled the growth anticipated on the basis of previous development. Also, 1 quadrupled and 4 more than doubled the normal increment for each individual age period.

We believe these responses sufficiently satisfactory to warrant the assumption that the relatively small doses of growth hormone employed in the 7 favorable cases are adequate to accelerate retarded growth.

In none of the cases treated for more than 1 year was there displayed any evidence of a refractory period, or a time at which response to therapy failed. In the 3 cases treated for 2 years or longer growth in the second year actually exceeded that of the first year. We have seen no phenomena which might be interpreted as representing a production of antihormone.

The behavior difficulty for which 7 of these patients were referred to the Clinic has satisfactorily cleared in 5 cases, and these patients are making good adjustments.

One boy with no delinquency applied voluntarily for treatment. The girl and one boy were referred because of repeated truancy. Four boys were convicted of repeated larcenies. Two were considered incorrigible, one of whom was also an habitual truant and petty thief. This last boy is the one who has failed to adjust satisfactorily. He is still a definite behavior problem, despite the fact that there has been no repetition of his thefts or truancy. The other patient, whose behavior has not improved appreciably, is also the case showing the least response to growth hormone therapy.

SUMMARY

Eight cases of endocrine growth deficiency (pituitary dwarfism) are presented, 7 males and 1 female. The age range was from 11 to nearly 16 years at onset of treatment. Anterior pituitary growth hormone and thyroid extract were employed concomitantly as therapeutic measures to accelerate growth. Treatment in 3 cases was continuous for 2 years or more, over 1 year in 4 cases, and for 8 months in 1 case. Relatively small doses of growth hormone (2 cc. antuitrin-G, 3 times weekly) apparently elicited favorable developmental response in 7 cases. In 1 case, increasing the dosage of growth hormone did not further accelerate the previous improvement in height increment. No phenomena were noted in this small series which would postulate the existence of a period refractory to treatment or an antihormone substance. Seven cases were serious behavior problems, and 5 of these have adjusted satisfactorily. The one case failing to adjust in behavior displayed no accelerated growth under growth hormone therapy.

Grateful appreciation is acknowledged to L. Maston, P. Papworth, F. Milstein, Mrs. J. Koch and Miss S. Preston (nurses), as well as other workers in the Clinic, who have kindly assisted in treating these patients, assembling and preparing the information presented herein.

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ASSOCIATION NOTICE

SCIENTIFIC PROGRAM OF THE TWENTY-SECOND ANNUAL MEETING

Hotel St. Francis, San Francisco, California

The Rôle of the Thyroid in Functional Colon Disorders. Felix Cunha, *San Francisco, Calif.*

Effect of Parathyroidectomy and Renal Function on the Action of Calciferol. F. A. McJunkin, M. C. Patras, R. D. Templeton and W. R. Tweedy, *Chicago, Ill.*

Diabetes Mellitus Associated with Hyperthyroidism. Daniel P. Foster and William L. Lowrie, *Detroit, Mich.*

Insulin Therapy in Mental Diseases. C. J. Kurth and D. V. Conwell, *Halstead, Kan.*

The Effect of Insulin Hypoglycemia on the Central Nervous System. Harold E. Himwich, Karl M. Bowman, Joseph Wortis and Joseph F. Fazekyas, *Albany and New York, N.Y.*

Experimental Obesity. Eaton M. Mackay, *San Diego, Calif.*

Pituitary Dwarfism Versus Diabetic Infantilism, Illustrated by a Case Report. James W. Sherrill, *San Diego, Calif.*

A Critical Statistical Comparison of Sixty-nine Pathologically Verified Cases of Simmonds's Disease with One Hundred Thirty-four Clinical Cases. Roberto F. Escamilla, *San Francisco, Calif.*

Infantilism with Congenital Webbed Neck and Cubitus Valgus. Henry H. Turner, *Oklahoma City, Okla.*

Studies Relating to Methods of Characterizing Two Gonadotropic Hormones, Follicle-Stimulator and Luteinizer. F. J. Saunders and E. H. Cole, *Davis, Calif.*

The Relation of the Anterior Pituitary to the Development of the Mammary Glands. Warren O. Nelson, *Detroit, Mich.*

Progestin Studies I. Pregnandiol Excretion. J. P. Pratt and R. F. Stover, *Detroit, Mich.*

The Therapeutic Use of the Sex Sterols in Functional Meno-Metorrhagia. E. C. Hamblen, *Durham, N.C.*

The Use of Testosterone Propionate in Functional Menorrhagia. Experimental Study of Twenty-five Cases Controlled with Endomentrial Biopsies. Samuel H. Geist, Udall J. Salmon and Joseph A. Gaines, *New York, N.Y.*

The Effect of Androgens on the Genital Tract of Immature Female Rats. Udall J. Salmon, *New York, N.Y.*

Androgens of Blood, Urine and Testes. D. Roy McCullagh and Walton O. Osborn, *Cleveland, Ohio.*

The Rôle of Biochemistry in Endocrinology. E. C. Kendall, *Rochester, Minn.*

The Diabetes of Bearded Women (Diabetes, Hirsutism and Suprarenal Tumor). E. Clare Shepardson and Edward Shapiro, *San Francisco, Calif.*

A Case of Arrhenoblastoma which Simulated Cushing's Disease. C. Kelly Canelo, *San Jose, Calif.*

Pseudo-Sexual Precocity, The Adrenal Cortical Syndrome in Girls. Report of Suc-

cessfully Operated Case and Review of the Literature. Anthony Reilly, H. Lisser and Frank Hinman, *San Francisco, Calif.*

Subclinical Adrenogenital Syndrome. S. J. Glass, *Los Angeles, Calif.*

Response to Cold Following Double Adrenalectomy. S. M. Horvath, *Oxford, Ohio.*

Adrenal Insufficiency Secondary to Pituitary Tumor. Frank N. Allan, *Boston, Mass.*

The Treatment of Addison's Disease with Adrenal Cortex Extract. W. O. Thompson, P. K. Thompson, S. G. Taylor III and W. S. Hoffman, *Chicago, Ill.*

Recent Studies in Cushing's Disease. Evelyn Anderson and Webb Haymaker, *Berkeley, Calif.*

Further Studies of Male Sex-Stimulating, Female Sex-Repressive Fractions of the Adrenal Glands of Cows, Steers and Bulls. F. M. Pottenger, Jr., *Monrovia, Calif.*

The Endocrine Aspect of Essential Hypertension and Diabetes Mellitus. James H. Hutton, James T. Case, William L. Culpepper, E. C. Olson and E. E. Madden, *Chicago, Ill.*

Diagnostic Value of Build in Menstrual Disorders and Obesity. Leona M. Bayer, *San Francisco, Calif.*

Endocrine Theories of Dysmenorrhea. C. F. Fluhmann, *San Francisco, Calif.*

Effect of Anterior Pituitary Sex Fraction upon the Development of the Human Uterus. Sheldon A. Payne, E. Kost Shelton and B. N. Tager, *Los Angeles, Calif.*

Observations Associated with Uterine Bleeding. Allan Palmer, *San Francisco, Calif.*

Antigonad Effect of Prolactin in Menorrhagia. George Joyce Hall, *Sacramento, Calif.*

Tuberculosis and the Female Sex Cycle. Emil Bogan, Miriam Hubbell and Josephine West, *Olive View, Calif.*

The Specific Dynamic Action in Castrated and Menopausal Women. William M. Moffat, *Santa Barbara, Calif.*

The Clinical Interpretation of the Endometrial Biopsy. Report of Findings in Three Hundred Cases. J. Kotz and Elizabeth Parker, *Washington, D.C.*

For further information about the meeting, see Page 386 of the March number.

CURRENT ENDOCRINE LITERATURE

COLLABORATORS

Fuller Albright
Wayne J. Atwell
Geoffrey Bourne
Israel Bram
John C. Burch
H. J. Deuel, Jr.
John C. Donaldson
Maurice H. Friedman
Murray B. Gordon
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A. E. Meyer
Warren O. Nelson
J. P. Pratt
A. T. Rasmussen
Elmer L. Sevringhaus
L. B. Shpiner
D. L. Thomson
R. L. Zwemer

ADVANCE ABSTRACTS

Relative effectiveness of testosterone-propionate and dihydroandrosterone-benzoate in the chick as indicated by comb growth. Breneman, W. R. To appear in this Journal.

The injection of dihydroandrosterone-benzoate and testosterone-propionate into the unoperated chick gave results with respect to comb growth which were contrary to those described in the literature for the capon. Generalisations concerning male hormone action, which have been based on treatment of capons, are inadequate when applied to the response observed in the normal chick. A survey of the results in 214 experimental and approximately 350 control birds showed that dihydroandrosterone-benzoate was more effective in producing comb growth than was testosterone-propionate. Testosterone-propionate elicited greater comb growth when given in a series of smaller doses than when the same amount was given in a single injection. The dihydroandrosterone-benzoate, to the contrary, was surprisingly effective when given in single injections. Comb growth was comparable to that produced by daily injections, and greater than that in most of the testosterone-propionate series. Combs continued to grow after the cessation of injections, and the data indicated that this continued growth was not a result of the retention and slow utilization of the injected hormone, because comb growth was distinctly less in chicks caponized when 5 days old and given male hormone than it was in the unoperated chicks which received injections. It is suggested that an additional factor was involved in the unoperated chick, perhaps the secretion of some androgenic substance. Development of other secondary sex characters was observed, and crowing occurred as early as the 11th day of age.

Post-adrenalectomy diuresis: effects of cortical extracts, salts and estrone. Gaunt, R., H. E. Potts and Eleanor Loomis. To appear in this Journal.

The food intake, water intake, urine output, and weight changes were measured in adult male adrenalectomized rats under various conditions. Rats which developed acute symptoms of adrenal insufficiency within two weeks or less following operation showed only slight, if any, diuresis. The water intake was reduced. The altered water exchange in these cases was not entirely due to inanition. Rats with chronic adrenal insufficiency developed a marked diuresis which apparently could last until terminal symptoms supervene. Cortical extracts in the relatively large doses needed for maintenance of normal appetite and growth did not completely remedy the altered water exchange. One % NaCl in drinking water maintained life, and a water exchange not significantly different from that induced by the same treatment in normal animals. One-tenth % KCl in the drinking water was toxic to adrenalectomized rats, and resulted in a diuresis much more severe than that seen in intact animals given the same treatment. A low salt diet in adrenalectomized rats reduced the life-span and, although the urine volume was less than in normal animals on this diet, it was very high in relation to the water intake. Theelin in doses of 100 I.U. per day was toxic to adrenalectomized animals, and produced a conspicuous diuresis. A low ratio of water intake to urine output accompanied all post-adrenalectomy conditions.

The effect of the anterior pituitary-like hormone on spermatogenesis in the human. Rubinstein, H. S. To appear in this Journal.

Studies bearing upon the effect of spermatogenesis in the human were carried out on 6 healthy adult males. It was found advantageous to determine the variation in sperm counts obtained at different times. Because the count was found to increase gradually through a period of 6 or 7 days following an ejaculation, control counts were listed for 1 and 6 or 7-day specimens. Injections of APL substance in dosage approximating 1000 R.U. weekly were administered intramuscularly 3 times weekly for a period varying from 5 to 9 weeks. Sperm specimens collected by condom or through masturbation were studied for volume, number per cc., total number, motility, viability and morphology, these last three showing no changes from the normal. The volume was found to be inconstant during the entire period of study. Total counts were, therefore, used for comparison.

It was found that in all cases, the total count was increased above normal after periods of treatment varying from 4 to 7 weeks, remaining high in all cases but one. With cessation of injections, the counts continued high in all cases, including the one in whom a drop had occurred during the treatment, for periods ranging between 2 to 5 weeks when they returned to normal ranges. Differences existing between previous reports are discussed.

Studies relating to time of human ovulation. III. During lactation. Lass, P. M., Jane Smelser and R. Kurzrok. To appear in this Journal.

Forty-seven women studied through their postpartum period had 194 fairly regular cycles. One hundred and six cycles (55%) were anovulatory or sterile in character, and the bleeding was not true menstruation since it did not come from a premenstrual endometrium. Eighty-two (45%) cycles were ovulatory in character, hence fertile, and the bleeding represented true menstruation.

Gonadotropic action of normal male urine extract on the dog. Leathem, J. H., and J. A. Morrell. To appear in this Journal.

An extract of normal male urine was found comparable to menopause urine extract in inducing estrus reactions in 11 of the 12 normal dogs tested. Other indications of gonadotropic activity in the manner of a follicle stimulator were ascertained by excessive follicle stimulation, in which the ovary increased in weight to as much as 8 times that of a normal anestrus ovary, the resorption of embryos in a pregnant animal and the failure to affect a castrate dog. Normal male urine extract was found capable of inducing all the external manifestations of estrus, namely, vulva swelling, hemorrhagic discharge and estrus as determined by acceptance of the male. In addition, endometrial hypertrophy and vaginal smear changes also resulted. Some specific differences in comparison to spontaneous estrus and estrus induced with menopause urine extracts are cited. Ovulation was determined by pregnancy in which one of the 5 dogs tested became pregnant, delivered and suckled two normal pups. Injection of follutein on the first day of induced estrus caused ovulation in the one case tested.

The effects of certain gonadal and gonadotropic hormones on the gestation period of the rat. Bunde, C. A. To appear in this Journal.

The luteinizing and follicle-stimulating fractions, as well as unfractionated pituitary extract, inhibit parturition when injected into pregnant rats during the later part of pregnancy. In all instances heavily luteinized, mulberry type ovaries are produced. A subminimal amount of unfractionated extract is able to inhibit parturition when hemin is added to it. Pregnant mare serum produces ovaries which contain many large follicles as well as corpora lutea, and it is not as effective for inhibiting parturition as is unfractionated pituitary extract. Two highly purified preparations and two methyl alcohol extracts of progestin, even in large amounts, were unable to definitely prolong gestation. It is concluded that gonadotropic substances inhibit parturition by acting through the ovaries but, since corpus luteum preparations did not prolong gestation, the effect of gonadotropic extracts is not merely an increase in progestin secretion.

Influence of adrenal cortex upon compensatory hypertrophy of the adrenal cortex. MacKay, E. M., and Lois Lockard MacKay. To appear in this Journal.

When one adrenal gland is removed the cortex of the remaining gland undergoes a compensatory hypertrophy. This compensatory hypertrophy is suppressed or prevented by the administration of adrenal cortex extract. It is probable that the hypertrophy is dependent upon stimulation by an anterior pituitary hormone, the production of which depends on the concentration of adrenal cortex hormone circulating in the organism. When the lack of this hormone follows unilateral adrenalectomy compensatory, hypertrophy does not ensue when

the stimulation by the anterior pituitary is prevented by supplying the deficiency in cortical hormone from outside sources.

The care and handling of the European bitterling as an experimental animal in endocrine research. Weisman, A. I., and C. M. Rothburd. To appear in this Journal.

The female bitterling test, a fish test for the presence of hormones in urine, is explained. Recently, reports have appeared which intimate that experiments performed on these fish yield no corroboration of the early workers, and that the fish have died while under study. It is essential when dealing with aquarian animals to know their physiological reactions just as well as we know the anatomy, physiology, etc., of the other more common laboratory animals. This preliminary knowledge has often been lacking in clinicians attempting to work with a new animal. The questions of water, temperature, hydrogen ion, habitat, toxicity, and other factors involved in fish research are summarized. Explanations based on the experimental environment of the fish are given for the slowness of corroboration and the death of the fish.

Menopause. A consideration of the symptoms, etiology and treatment by means of estrogens. Wiesbader, H., and R. Kurzrok. To appear in this Journal.

Two hundred patients were successfully treated for menopause symptoms by means of estrogens, an ether-alcohol extract of the whole ovary and calcium. The best results were obtained in patients in whom the menopause was complete, that is, in whom menstruation had ceased completely. Uterine bleeding (not menstruation) may result from such treatment. The significance of this is discussed.

ADRENALS

Magnesium and carbohydrate metabolism. Corkill, A. B., and A. H. Ennor, Med. J. Australia 1:113. 1938.

Rabbits were imprisoned in a plaster cast and $MgCl_2 \cdot 6H_2O$ infused intravenously by means of a glass cannula inserted into an ear vein. The results of previous workers, that the infusion of $MgCl_2$ in this manner caused an increase of liver glycogen was not confirmed. A hyperglycemia was found, which could not be produced in adrenalectomized animals. Infusion of NaCl in the same manner did not cause a hyperglycemia.—G. B.

Cardiac modifications in adrenalectomized toads (Modificaciones cardíacas de los sapos suprarrenoprivos). Fustinoni, O., and V. H. Cicardo, Rev. Soc. Argent. de biol. 13:250. 1937.

Toads were adrenalectomized by cauterization. They survived 1-6 days. Bradicardia was observed in the final stages. Heart glycogen was significantly decreased in the adrenalectomized, compared to controls with kidneys cauterized but adrenals intact. When adrenal asthenia was pronounced, the excitability was tested in hearts stopped by a Stannius ligature, by stimulating them with condensor discharges. The rheobase and chronaxie were definitely increased. The rheobase of the vagus nerve was decreased, and its chronaxie showed variable changes. Electrocardiograms were obtained by placing one electrode in the mouth, and the other under the skin in the ventral region. The *R* deflection was of longer duration but less height, independently of temperature and heart frequency.—J. T. L.

Investigations of the gonadotropic effect of the adrenal cortex extract (Untersuchungen über die gonadotrope Wirkung von Nebennierenrindenextrakten). Hoffman, F., Ztschr. f. Geburtsh. u. Gynäk. 115:416. 1937.

A gonadotropic substance different from cortin was extracted from the adrenal cortex of cattle. Fresh adrenal cortex was extracted with water. Acetone was added and the solution iced over night. The precipitate was washed with acetone and ether, and then extracted with water. Solids were removed by centrifuge. Protein was removed by trichloroacetic acid. Acetone was added and the precipitate extracted with water. Injection of extract equivalent to 1 gm. of fresh tissue stimulated follicle growth, and increased the size of the ovaries in infantile white rats. The optimum effect came in 65-90 hours, but with prolongation of the treatment the ovaries regressed. Combined with anterior lobe or prolan, the follicle-stimulating effect was greater than with either substance alone. The gonadotropic effect is less for the adrenal extracts than for the anterior lobe.—M. R. White.

ENDOCRINE GENERAL

Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty. Albright, F., A. M. Butler, Aubrey O. Hampton and Patricia Smith, New England J. Med. 216:727. 1937.

A syndrome was described in 4 females and 1 male which was characterized by multiple bone cysts having a distribution suggesting a relation to nerve roots or to an embryological defect in the myotomes, by areas of pigmentation which have a distribution suggesting some connection with the bone cysts, and by precccious puberty in females but apparently not in males. The precocity is unusual, in that it does not lead to sterility or other endocrine disturbances, and is thought to be due to disturbance of the follicle-stimulating hormone of the anterior pituitary. The bone lesions consist of multiple circumscribed areas of osteitis fibrosa with normal bone elsewhere. The lesions differ from those due to hyperparathyroidism in that they are spotty rather than generalized, and are not accompanied by changes in calcium and phosphorus metabolism.—J. M. L.

The effect of amniotin and antuitrin-S in diabetes insipidus. Blotner, H., New England J. Med. **217**:592. 1937.

Seven patients with diabetes insipidus were studied. In 5 of these 20,000 U of amniotin was injected daily for 10 days. In 4 cases 1 cc. of antuitrin-S was injected daily or every other day for a period of 2 months. No decrease in the volume of urine excreted was obtained, although the sugar tolerance in 4 cases was increased.—J. M. L.

Treatment of menorrhagia and metrorrhagia by endocrine products. Burch, J. C., G. S. McClellan, J. W. Simpson, C. D. Johnson and E. T. Ellison, J. A. M. A. **109**:1869. 1937.

Functional menorrhagia and metrorrhagia are symptoms of an ovarian disturbance, either primary or secondary to diseases of the pituitary or thyroid, or secondary to some constitutional disease affecting one or more components of the endocrine system. In the treatment of menorrhagia and metorrhagia with endocrine products an accurate diagnosis is essential. The underlying endocrine condition, as well as the general constitutional state of the patient is determined. The degree of ovarian deficiency can be estimated from a study of the endometrium. The existing endocrine lesions should be treated with specific measures. The most satisfactory results are obtained in hypothyroidism. In the authors' experience it has been best to start in these cases with from ½ to ¾ grain (0.03 to 0.05 gm.) of U.S.P. desiccated thyroid daily. After a period of 2 weeks, the dose is adjusted according to the patient's response. The adjusted dose is given for 2 weeks and the procedure repeated. The basal metabolism is determined at the end of 6 weeks and the dose of thyroid is increased until the metabolism is at or near normal, or until undesirable symptoms occur. If such symptoms do occur, the dose is reduced to the level at which the greatest effect can be obtained with the least undesirable reaction. The final principle in the treatment of menorrhagia and metrorrhagia with endocrine products is the realization that surgery and irradiation produce only a symptomatic cure. They have a definite and important place in treatment, but the underlying pathologic condition is still present and usually demands further treatment. Neglect of this final principle has been almost universal, and every gynecologist has patients who are cured of their menstrual disorder but who still have their primary disease.—Abst., A. M. A. Service.

GONADS

Relation between estrin and thrombocytes in animal experiments (Beziehungen zwischen Follikelhormon und Thrombocyten im Tierversuch). Bareuther, A., and Else Schabbel, Klin. Wchnschr. **16**:1677. 1937.

Daily injections of 10,000 or more I.U. of estrin-benzoate into female dogs led to the appearance of the typical blood picture of thrombocytopenic purpura, with prolonged bleeding time, normal clotting time, and also weakness anorexia, multiple hematomata in the neck and extremities, tarry stools, and alveolar peri-dental bleeding. Death finally resulted, and at autopsy marked hemorrhage was noticed in the gastrointestinal tract. The onset of the disease depended on the size of the daily dose, appearing after 10 or 11 injections of 50,000 U daily, but not until the 25th injection of 10,000 U. Simultaneous injection of 125 B.U. of androsterone did not protect one female against the action of estrin, though it seemed to afford protection to one of two males so injected. In two dogs, estrin was injected until symptoms of purpura appeared. The therapeutic administration of large doses of liver extract ameliorated the symptoms and corrected the blood picture, despite continued estrin injections. However, the liver extract did not prevent the eventual death of the animals on this regime.—M. H. F.

Concerning the thyreotrophic hormone in pregnancy (Über thyreotropes hormonein der schwangerschaft). Bonilla, F., and H. Kramann, Monatschr. f. Geburtsh. u. Gynäk. **106**:24. 1937.

Fifty gm. of placenta, from each of 10 normal pregnancies, and 5 eclamptic or pre-

eclamptics yielded no thyreotropic hormone when tested on young guinea pigs, according to the method of Loesser.—M. R. White.

Synergic and antagonistic effect of the hypophysis of fish, batrachians and birds on the gonadotropic effect of urine extracts (Acción sinérgica y antagónica gonadotrópica-hipofisaria en peces, batracios y aves). Del Castillo, E. B., and A. Novelli, Rev. Soc. argent. de biol. **13**:448. 1937.

Infantile rats (30-50 gm. weight) received for 5 days daily subcutaneous injections of, *a*), 1 cc. urine from 4th-5th month pregnant women; *b*), 2 glandular lobes of the hypophysis of the species studies, suspended in saline; *c*), 2 glandular lobes suspended in pregnancy urine. Litter mates were observed as normal controls. The weights of the ovaries from the different groups were compared. The pituitaries from the fishes used had an antagonistic effect on the gonadotropic activity of the urine. Anterior lobe of toad hypophysis had a synergic effect, and hen hypophysis did not modify the gonadotropic effect of pregnancy urine.—J. T. L.

Effect of oestrone and testosterone on the male sexual organs (Acción de la Estrona y Testosterona sobre el aparato sexual masculino). Del Castillo, E. B., and A. Pinto, Rev. Soc. argent. de biol. **13**:426. 1937.

Adult male rats (13) received daily 15 U estrone for 30 days. Six showed testicular atrophy and absence of spermatogenesis, but the intersticial cells were well preserved or even hypertrophied; the epithelium of the seminal vesicles atrophied, with apparent hypertrophy of the muscular coat. The penis was reduced in weight. The other 7 rats had normal sexual organs. A more prolonged treatment (3-4 months) produced testicular atrophy in 10-16 rats; 6 of these also had atrophy of the seminal vesicles and the prostate, and the penis was slightly smaller. A larger dose (30 U once a month) produced testicular atrophy in 4-6. A very large dose (50 U for 12 days) produced an increase in weight in the testicles, seminal vesicles and prostate, with histological aspect of increased spermatogenesis. This same dose given to castrates retarded the involution of the prostate and seminal vesicles. Testosterone propionate (2 mg. daily for 12 days) produced sexual excitement (frequent coitus and ejaculation) and considerable increase in weight of prostate and seminal vesicles. The same treatment plus 50 U estrone in castrated rats gave an even larger increase in weight of prostate and seminal vesicles. In guinea pigs large doses of estrone (50 U) increased the weight of the prostate and seminal vesicles; in castrates, so treated, the involution was retarded. Testosterone increased the weight of the sexual organs of the guinea pig; when given with estrone the increase was greater.—J. T. L.

HYPOPHYSIS

Effect of anterior pituitary extract on liver and muscle fat (Acción del extracto anterohipofisario sobre la grasa hepática y muscular). Foglia, V. G., and P. Mazzocco, Rev. Soc. argent. de biol. **13**:301. 1937.

Anterior pituitary extract, with diabetogenic activity produced in dogs a considerable increase in liver fat, similar to that observed after pancreatectomy; simultaneously liver glycogen increased, contrary to what occurs in pancreatic diabetes. Thyroidectomy and removal of the adrenal medulla did not modify this effect of the extract on liver fat (muscle fat was also increased by the extract, but less considerably than the liver fat), and muscle glycogen was not diminished by the extract in normal dogs. In pancreatectomized dogs it produced a considerable decrease. Hyperglycemia and glycosuria was produced by the extract, but to a considerably less degree than that produced by pancreatectomy. The extract did not increase the hyperglycemia and glycosuria of the pancreatectomized dogs, it increased ketonemia and ketonuria, but less so than pancreatectomy; and it increased ketonemia and ketonuria considerably in pancreatectomized animals. The extract increased lipemia more considerably than pancreatectomy; and in pancreatectomized dogs it produced a very high lipemia. Variations in phospholipids and cholesterol were not important. Since similar extracts of muscle, kidney liver, adrenals and testes did not produce these effects of the anterior pituitary extracts, they can be considered as specific.—J. T. L.

The action potential of the frog's hypophysis exposed to the dark (Ueber die Aktionsströme an der Froschhypophyse bei Aufenhalt im Dunkeln). Hasama, B., Arch. f. d. Ges. Physiol. **239**:400. 1937.

After removing the anterior lobe of the hypophysis of the frog, an action current can be recorded from an electrode placed on the exposed pars intermedia. When the frog is placed in the dark there is a sudden increase in the negative potential which gradually recedes as the melanophores expand.—A. G.

Effect of oestrone on the gonadotropic activity of toad (*B. arenarum*) pituitary [Influencia de la administración de oestrona sobre el poder gonadotropo de la hipófisis de sapo (*Bufo arenarum*)]. Freire, M. A., Rev. Soc. argent. de biol. 13:500. 1937.

Estrone (60 U daily for 14-20 days) was injected subcutaneously in toads. The pituitaries were then subcutaneously implanted (2 for every animal) into female toads. Ovulation occurred as when the pituitaries from normal controls was injected.—J. T. L.

What is the support for the assumption of cortico-adrenotropic hyperpituitarism on the basis of morphologic evidence in the human? Kraus, E. J., Klin. Wchnschr. **16**:1528. 1937.

The author recalls previous reports of the high degree of association of small cytic ovaries, augmented prolan excretion, and hypertrophy of the pituitary in cases of chronic intracranial tension, and also the reported association of markedly increased lipoid in the adrenals in cases of pituitary adenoma. The author presents 12 cases of chronic intracranial tension, with associated lipoid change in the adrenals, or marked weight increases in the adrenals, or both. Such changes are not necessarily associated with increased size of the pituitary. Without citing detailed figures, the author states that adrenal hypertrophy occurs in about 85% of cases with chronic increased intracranial pressure.—M. H. F.

PANCREAS

Histological studies on the diencephalic-pituitary system and the endocrine glands in diabetes mellitus (Ricerche istiologiche sul sistema diencefaloipofisario e sulle ghiandole endocrine in casi di diabete mellito di origine pancreatica). Bini, G., Arch. per le sc. med. **64**:511. 1937.

In pancreatic diabetes the hypophysis was found to show sclerotic areas, atrophy, rarefaction of nuclei, necrosis, hemorrhages, hyaline tumefaction of connective tissue, cystic degeneration of the anterior lobe and occasionally basophilic hyperplasia of the nervous lobe. In the diencephalon alterations of the suprachiasmatic nuclei, hemorrhages into the third ventricle and atrophy of the paraventricular nucleus were observed. These lesion are ascribed to general toxicosis caused by pancreatic insufficiency. The disturbances in sugar metabolism are not ascribed to the diencephalon.—A. E. Meyer.

Cytologic modifications in the liver in experimental pancreatic and pituitary diabetes (Variaciones citológicas del hígado en las diabetes pancreática e hipofisiaria experimental). De Robertis, E., Rev. Soc. argent. de biol. 13:336. 1937.

Pancreatectomy in dogs produced the following modifications in the structure of the liver: decrease in cell volume uniformly throughout the lobule; disappearance of glycogen; increase in fats more or less uniformly distributed. When the infiltration was considerable, the droplets could occupy the whole cytoplasm, especially in the periphery of the lobule. The condrioma was granular and compact, the alterations being more marked 24 hours after pancreatectomy. In dogs made diabetic through injection of anterior pituitary extract there was a considerable increase in liver cell volume, due to an increase in paraplastic substances. A slight increase in glycogen and a considerable one in fats were both most marked in the periphery of the lobules. The condrioma was modified considerably in relation to the accumulation of glycogen and fat. Thyroidectomy, sectioning of the splanchnics, and removal of the adrenal medulla, did not modify the activity of the extract. Extracts of muscle, kidney, testes, liver and adrenals did not produce these alterations in the liver cells. Pancreatectomized dogs injected with the extract showed a great increase in liver fats, a disappearance of glycogen, and modifications in the condrioma. Insulin reduced the intensity of the effect of the extract.—J. T. L.

Protein metabolism and blood proteases in pancreas diabetes (Ricambio proteico e proteinasi ematiche nel diabete pancreatico). Ferranti, F., and E. Slavich, Arch. per le sc. med. **64**:297. 1937.

High blood protease is almost constantly found in diabetes. Insulin causes a drop of the protease to a low level, even if the hypoglucemia is arrested with glucose or adrenalin. The high glood protease does not originate from the pancreas. It is probably related to an increased protein metabolism and the drop after insulin is a consequence of an inhibiting action of this hormone on the nitrogen metabolism.—A. E. Meyer.

Effect of prolonged fasting and of sugar on endocrine pancreatic function (Acción del ayuno prolongado o una dieta azucarada sobre la función endócrina del páncreas). Foglia, V. G., Rev. Soc. argent. de biol. **13**:385. 1937.

After a 2-3 weeks' fast, the pancreas was removed from dogs and grafted into the neck of diabetic (pancreatectomized) dogs by connecting the artery and vein of the graft with the carotid and jugular of the recipient. The blood sugar of the recipient decreased to the normal level, as occurred when the pancreas from normal dogs was grafted in 4 experiments; in 3 others the blood sugar decreased slightly or not at all. Sugar was added to a meat diet (100 gm. daily for 15 days in 2 experiments, and 30 gm. daily for 37 days in 2 experiments); the pancreas grafted into diabetic dogs produced a decrease in the glycemia in 3 cases and no decrease in 1.—J. T. L.

THYROID

Liver function in hyperparathyroidism as determined by the hippuric acid test. Bartes, E. C., and H. J. Perkin, New England J. Med. **216**:1051. 1937.

The liver function was tested in 66 patients before and after thyroidectomy by determining the hippuric acid excretion after the ingestion of 5.9 gm. of sodium benzoate. A subnormal excretion was found in 72% of the patients with hyperthyroidism requiring a single operation, and in 96% of those requiring a two-stage operation. In 16 patients having adenomatous goiter with hyperthyroidism, 81% had subnormal excretion values. In most cases an increase in hippuric acid excretion followed pre-operative improvement, and especially in the primary hyperthyroid cases. After operation there was a decrease in excretion. A close correlation was found between hippuric acid excretion and increase in blood cholesterol during pre-operative treatment.—J. M. L.

Vitamin C and thyrotoxic creatinuria (Vitamin C und thyreotoxische Kreatinurie). Fischer, G., and C. Oehme, Klin. Wchnschr. **16**:1453. 1937.

Colorimetric creatine determinations on the urine of rats injected with 35 gamma of thyroxin daily for 4 to 14 days showed marked increase in creatine excretion. The simultaneous administration of 40 mg. of vitamin C largely prevented this increase. Cortin, which has been reported to protect against thyroxin in regard to metabolic rate increase, was not effective in preventing the thyrotoxic creatinuria. Like the glycogen loss from the liver during hyperthyroidism, this creatinuria is inhibited by vitamin C, but not by cortin.—M. H. F.

The action of thyroid substance on the liver function of elimination studied by the congo red test (Azione della sostanza tiroidea sulla funzione epatica di eliminazione studiata con la prova del rosso congo). Fossati, C., Rev. sud-am. de endocrinol. **21**:23. 1938.

The elimination of congo red by the liver of normal individuals is accelerated by the medication with thyroid substance. The elimination of the dye, retarded in liver pathology such as catarrhal jaundice or cirrhosis, can be improved by thyroid treatment and even be brought back to normal values.—A. E. Meyer.

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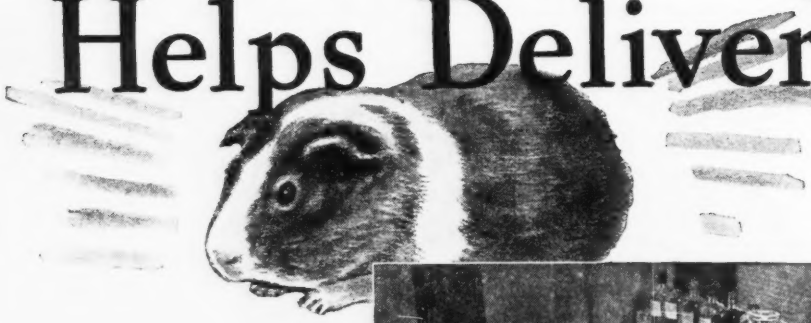

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